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Intravenous Nicardipine

Its Use in the Short-Term Treatment of Hypertension and Various Other Indications

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Data Selection

Sources: Medical literature published in any language since 1980 on 'nicardipine', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were 'nicardipine' and 'intravenous'. AdisBase search terms were 'nicardipine' and ('intravenous' or 'IV' in title). Searches were last updated June 24 2006.

Selection: Studies in patients who received intravenous nicardipine. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Intravenous nicardipine, hypertension, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Nicardipine is a water soluble calcium channel antagonist, with predominantly vasodilatory actions.

Intravenous (IV) nicardipine (Cardene® IV), which demonstrates a relatively rapid onset/offset of action, is used in situations requiring the rapid control of blood pressure (BP). IV nicardipine was as effective as IV nitroprusside in the short-term reduction of BP in patients with severe or postoperative hypertension. A potential role for IV nicardipine in the intraoperative acute control of BP in patients undergoing various surgical procedures (including cardiovascular, neurovascular and abdominal surgery), and in the deliberate induction of reduced BP in surgical procedures in which haemostasis may be difficult (e.g. surgery involving the hip or spine) was demonstrated in preliminary studies. Preliminary studies also indicated the ability of a bolus dose of IV nicardipine to attenuate the hypertensive response, but not the increase in tachycardia, after laryngoscopy and tracheal intubation in anaesthetised patients. In large, well designed studies, IV nicardipine prevented cerebral vasospasm in patients with recent aneurysmal subarachnoid haemorrhage; however, overall clinical outcomes at 3 months were similar to those in patients who received standard management. Small preliminary studies have investigated the use of IV nicardipine in a variety of other settings, including acute intracerebral haemorrhage, acute ischaemic stroke, pre-eclampsia, acute aortic dissection, premature labour and electroconvulsive therapy.

In conclusion, the efficacy of IV nicardipine in the short-term treatment of hypertension in settings for which oral therapy is not feasible or not desirable is well established. The ability to titrate IV nicardipine to the tolerance levels of individual patients makes this agent an attractive option, especially in critically ill patients or those undergoing surgery. Potential exists for further investigation of the use of this agent in clinical settings where a vasodilatory agent with minimal inotropic effects is appropriate.

Pharmacological Properties

Nicardipine is a dihydropyridine calcium channel antagonist, with greater selectivity for L-type calcium channels in vascular smooth muscle than cardiac myocytes. Nicardipine demonstrates strong coronary and cerebral vasodilatory activity. It induces relatively rapid changes in BP, with minimal inotropic cardiac effects and no significant venodilatory action. The vasodilatory effects of nicardipine appear to be greater in patients with hypertension than in healthy normotensive volunteers. Nicardipine is highly lipophilic.

In patients with coronary artery disease, with and without impaired left ventricular function, IV nicardipine (with or without β-adrenoceptor antagonists) increased cardiac output, stroke volume and left ventricular ejection fraction, but had no significant effect on left ventricular end-diastolic pressure.

The pharmacokinetics of a continuous infusion of IV nicardipine or a bolus dose of IV nicardipine were linear in patients with mild to moderate hypertension. Rapid dose-related increases in plasma concentrations of nicardipine occurred during the first 2 hours after initiation of a 48-hour continuous infusion of IV nicardipine. Thereafter, the nicardipine concentration rose more slowly and took 24–48 hours to reach steady state. Nicardipine plasma concentrations declined triexponentially after an IV infusion, with an initial rapid distribution half-life ($t_{1/2}\alpha$ 2.7 minutes), followed by an intermediate elimination half-life ($t_{1/2}\beta$ 44.8 minutes) and a slow terminal elimination half-life ($t_{1/2}\gamma$ 14.4 hours). Nicardipine is highly bound to plasma proteins (>95%) over a wide range of concentrations. Nicardipine metabolism occurs mainly in the liver, primarily by cytochrome P450 (CYP)2C8, CYP2D6 and CYP3A4 enzyme isoforms. Excretion occurred in approximately equal proportions in the urine (49%) and faeces (43%), with no unchanged drug excreted.

Therapeutic Efficacy

A continuous infusion of IV nicardipine was as effective as a continuous infusion of IV nitroprusside in the reduction of BP in patients with severe hypertension (systolic BP >200mm Hg, diastolic BP >120mm Hg), with a similar proportion of patients (≥93%) achieving the therapeutic BP target within a similar timeframe (approximately 60 minutes).

IV nicardipine was as effective as IV nitroprusside in effectively controlling postoperative hypertension in patients who had undergone either cardiac or noncardiac surgery. However, with IV nicardipine, compared with IV nitroprusside, the time required to reach a therapeutic response was significantly less. Data from a number of preliminary studies support the intraoperative efficacy of IV nicardipine in the acute control of BP in patients undergoing various surgical procedures (including cardiac surgery, intracranial aneurysm clipping and abdominal surgery). IV nicardipine was effective in inducing deliberate hypotension (mean arterial pressure [MAP] 55–60mm Hg), and consequently limiting blood loss during specified surgical procedures in which surgical haemostasis may be difficult to achieve (e.g. surgery involving the hip or spine); once the infusion had ceased, the time to return to baseline MAP was longer with IV nicardipine than IV nitroprusside. Bolus IV nicardipine attenuated the hypertensive response, but not the occurrence of tachycardia, after laryngoscopy and tracheal intubation in normo- or hypertensive patients who had undergone induction anaesthesia. IV nicardipine was also effective in attenuating increases in BP during anaesthesia emergence and tracheal extubation.

IV nicardipine prevented cerebral vasospasm in patients with recent aneurysmal subarachnoid haemorrhage, with a reduced need for prophylactic intentional hypervolaemia/induced hypertension. However, overall clinical outcomes at 3 months were similar to those in patients who received standard management. Data from small preliminary studies indicated that IV nicardipine had beneficial effects in patients with acute intracerebral haemorrhage and acute ischaemic stroke.

Preliminary data also indicate that IV nicardipine effectively managed hypertension in pregnant women with pre-eclampsia, paediatric patients in the perioperative or intensive care settings, elderly hypertensive patients and patients with acute aortic dissection. In addition, IV nicardipine had beneficial effects on haemodynamic parameters in patients with acute heart failure. When administered in combination with labetalol, a bolus dose of IV nicardipine prevented the acute haemodynamic response to electroconvulsive therapy.

Tolerability

IV nicardipine was generally well tolerated in large well designed trials in patients requiring the short-term treatment of hypertension, with adverse events generally being non-serious and mostly the expected consequences of vasodilation. Headache, hypotension, nausea, vomiting and tachycardia were the most commonly reported adverse events, with the presence of adverse events occasionally requiring the adjustment of the dosage.

A continuous infusion of IV nicardipine for up to 14 days was generally well tolerated in a well designed trial in patients with aneurysmal subarachnoid haemorrhage, with hypotension occurring in 35% of IV nicardipine recipients and 18% of placebo recipients.

IV nicardipine was generally better tolerated than IV nitroprusside in patients requiring the acute control of hypertension in randomised, open-label, multicentre trials.

The tolerability of IV nicardipine in children or pregnant women has not been established in well designed trials. However, IV nicardipine was generally well tolerated in small, open-label studies in these patients.

1. Introduction

The ideal agent for use in the short-term treatment of hypertension is one that can be administered intravenously and readily titrated so that tight control over blood pressure (BP) and BP reduction can be achieved. The agent should be readily constituted, easily administered, have a short half-life ($t_{1/2}$) and have minimal adverse events.

Nicardipine, a dihydropyridine calcium channel antagonist, is a vasoselective agent with minimal negative cardiac inotropic effects.[1] It is water soluble and can be administered by the intravenous (IV) route.

An IV formulation of nicardipine (Cardene® IV)[1] has been approved in the US for the short-term treatment of hypertension when oral therapy is considered undesirable or not feasible.[2] This review focuses on the efficacy and tolerability of IV nicardipine in this indication, with a brief overview of the use of IV nicardipine in various other settings.

2. Pharmacodynamic Properties

The pharmacodynamic effects of nicardipine are well established.[3,4] A summary of the pharmacodynamic properties of IV nicardipine is presented in table I.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Summary of pharmacodynamic effects of intravenous nicardipine

Vascular/haemodynamic

↓ Transmembrane influx of calcium ions into the cardiac and smooth muscle without altering serum calcium concentrations[2]

↓ Systemic vascular resistance[3,8,11,15,16]

↓ Systolic BP, diastolic BP and MAP[8,10,16-20] (see section 4)

Minimal venodilatory effect[11,21]

Antispastic effects in radial artery *in vitro*[22,23]

↑ Membrane-stabilising action related to its lipophilic nature *in vivo*[24]

Cardiac

↑ Heart rate, secondary to reflex sympathetic activation[2,3,8,10]

↑ Vasodilation in healthy[3,4,12,15,25] and stenotic[26] coronary arteries

↑ Coronary blood flow[11,12,25-27]

Low incidence of no-flow during percutaneous coronary interventions[28]a

↑ Cardiac output, stroke volume and left ventricular ejection fraction, but no/little change in left ventricular end-diastolic pressure, in pts with CAD and normal or moderately abnormal left ventricular function (including those receiving β blockade)[8,11,16,20,27]

↑ Cardiac output, stroke index and cardiac index and improved pulmonary wedge pressure during rest and exercise in pts with congestive heart failure and impaired left ventricular function[11,29,30]

↑ Peak left ventricular diastolic early filling velocity, independent of changes in heart rate[31]

↓ Myocardial ischaemia during transient occlusion of the proximal left anterior descending coronary artery[32]

↓ Left ventricular lactate production in pts with angina pectoris[33]

No detrimental effects on cardiac conduction system.[5,11] No effect on atrioventricular or sinus node conduction time *in vivo*.[3,4,11] No significant effects on PR interval, QRS complex or the QT interval, PA, AH and HV intervals during His-bundle electrocardiography *in vivo*[11]

Cerebrovascular

↓ Cerebral vascular resistance[4]

Did not increase ICP compared with placebo in pts with severe head injury[34]

↓ Symptomatic and angiographic evidence of vasospasm in pts with recent aneurysmal subarachnoid haemorrhage[35-39] (table VII)

↑ Cerebral blood flow in ischaemic areas and the middle cerebral artery[4,13]

↑ Cerebral blood flow in the internal carotid artery[40,41] and local cerebral blood flow[41] during aneurysm clipping

Attenuated cerebral pressure autoregulation during propofol-fentanyl anaesthesia in pts undergoing surgery[42]

No change in perihaematoma regional cerebral blood flow,[43] or middle cerebral arterial blood flow velocity[44] in patients with intracranial haemorrhage; ↓ ICP but remained above normal values[44]

Renal

↓ Renal vascular resistance after a bolus dose in healthy volunteers; GFR, renal plasma flow and the filtration rate were unchanged[2]

↓ Total renal vascular resistance and ↑ GFR and renal blood flow in diabetic pts with hypertension and mild to moderate nephropathy[45]

↑ Sodium and phosphate excretion[3,45-49]

Endocrine/Metabolic

No effect on glucose-stimulated insulin secretion[3,50]

No effect on follicle-stimulating hormone, luteinising hormone, prolactin or thyroid-stimulating hormone levels[3]

↓ Aldosterone response,[51] but no effect on aldosterone response to angiotensin II;[52] ↑ plasma renin activity in pts with salt-resistant hypertension[51]

a Intracranial administration.

AH = conduction time from low right atrium to His-bundle deflection or atrioventricular nodal conduction time; **BP** = blood pressure; **CAD** = coronary artery disease; **GFR** = glomerular filtration rate; **HV** = conduction time through the His bundle branch-Purkinje system; **ICP** = intracranial pressure; **MAP** = mean arterial pressure; **PA** = conduction time from high to low right atrium; **pts** = patients; ↑ indicates significant increase; ↓ indicates significant decrease.

Nicardipine differs from nifedipine by having a tertiary amine structure added to the ester side chain at position three of the hydropyridine ring and a nitro group moved to the meta position of the phenyl

ring.[5] These differences make nicardipine 100 times more water soluble and more resistant to photoactivation than nifedipine. Consequently, nicardipine can be administered as an IV solution. Nevertheless, the manufacturer recommends that the ampoules containing nicardipine for IV administration are protected from light until they are ready for use.[2]

Nicardipine has high affinity (log equilibrium dissociation constant 9.7) for the dihydropyridine binding site and inhibits the L-type calcium channel.[1] These channels are widely distributed in the cardiovascular system, particularly in the myocardium and vascular smooth muscle, where they regulate calcium influx, thereby controlling muscular contraction.[6] Nicardipine binds to a site on the transmembrane segments of the α_1-subunit of the L-type calcium channel and stabilises the inactivated state of the channel.

Nicardipine demonstrates a greater selectivity for L-type calcium channels in vascular smooth muscle (log concentration required to inhibit 50% of a mechanical response [pIC_{50}] in mesenteric artery 8.20) than cardiac myocytes (pIC_{50} 7.16) *in vitro*.[1] The potency of nicardipine against coronary vascular smooth muscle was even greater (pIC_{50} 8.96).

The selectivity for arterial and especially cardiac arterial vascular smooth muscle is reflected in relatively large and rapid changes in BP,[7] with minimal inotropic changes in cardiac function that are thought to be secondary to baroreflex-induced adrenergic stimulation.[8] Systemic vasodilation acts to reduce myocardial oxygen demand and leads to a reduction in determinants of afterload (table I).[3,9,10] In addition, minimal changes in mean pulmonary capillary wedge pressure, pulmonary arterial pressure and right atrial pressure suggest no significant venodilatory action.[11] Following bolus coronary artery infusion, it caused a greater increase in coronary blood flow velocity and had a longer duration of effect than other calcium channel antagonists (diltiazem and verapamil) in patients with coronary artery disease.[12]

Preclinical studies demonstrate that IV nicardipine crosses the blood-brain barrier, and exerts a vasorelaxing action on cerebrovascular smooth muscle.[13] Nicardipine is almost completely pronated in an acid environment, allowing more rapid accumulation in ischaemic tissue than normoperfused cerebral tissue. Evidence of the cerebrovascular activity of IV nicardipine in clinical studies is summarised in table I and section 4.3.

The vasodilatory effects of nicardipine appear to be greater in patients with hypertension than in healthy normotensive volunteers.[14]

3. Pharmacokinetic Properties

3.1 Absorption and Distribution

The pharmacokinetics of a continuous infusion of IV nicardipine 0.5–4.0 mg/h[17] or a bolus dose of IV nicardipine 0.125–7mg[53] were linear in patients with mild to moderate hypertension.[2] The mean pharmacokinetic parameters of IV nicardipine are reported in table II.

Rapid dose-related increases in plasma concentrations of nicardipine occurred during the first 2 hours after initiation of a 48-hour continuous infusion of IV nicardipine 0.5–4.0 mg/h.[2,17] Thereafter, the nicardipine concentration rose more slowly and took 24–48 hours to reach steady state.[2] Values for peak plasma concentration (C_{max}), steady-state plasma concentration (C_{ss}) and area under the plasma concentration-time curve (AUC) were dose-related (figure 1).[17]

C_{max} occurred 1 minute after administration of bolus doses of IV nicardipine in patients with mild to moderate hypertension, with a linear relationship between the dose of nicardipine and peak plasma concentration.[53]

Nicardipine is highly bound to plasma proteins (>95%) over a wide range of concentrations.[2]

3.2 Metabolism and Elimination

Nicardipine metabolism occurs primarily in the liver through the cytochrome P450 (CYP) enzyme system, primarily by the CYP2C8, CYP2D6 and CYP3A4 isoforms.[54]

Table II. The pharmacokinetics of intravenous (IV) nicardipine. Mean values of pharmacokinetic parameters in a randomised, double-blind, placebo-controlled trial in 37 patients with mild to moderate hypertension receiving a continuous IV infusion of nicardipine 0.5–4.0 mg/h for 48 hours[17]

Parameter	Mean value
Maximum plasma concentration (ng/mL)[a]	184
Plasma concentration at steady state (ng/mL)[a]	157
Area under the plasma concentration-time curve (ng • h/mL)[a]	7511
Volume of distribution (L/kg)[a]	8.3
$t_{1/2\alpha}$ (min)[b]	2.7
$t_{1/2\beta}$ (min)[b]	44.8
$t_{1/2\gamma}$ (h)[b]	14.4
Clearance (L • h/kg)[a]	0.34

a 4.0 mg/h; noncompartmental analysis.

b Combined values for 0.5–4.0 mg/h; three-compartmental model.

$t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$ = elimination half-life; $t_{1/2\gamma}$ = terminal elimination half-life.

Nicardipine plasma concentrations declined triexponentially after an IV infusion (table II), with an initial rapid (α) distribution half-life ($t_{1/2\alpha}$ 2.7 minutes), followed by an intermediate elimination (β) half-life ($t_{1/2\beta}$ 44.8 minutes) and a slow terminal elimination (γ) half-life ($t_{1/2\gamma}$ 14.4 hours).[17]

Nicardipine is excreted primarily in the bile and faeces; after coadministration of an IV dose of [^{14}C]nicardipine plus 8-hourly oral nicardipine 30mg to healthy volunteers, 49% of the radioactivity was recovered in the urine and 43% was recovered in the faeces.[55] None of the dose was excreted as unchanged drug.[2]

3.3 Special Patient Populations

In patients with hepatic disease, plasma concentrations were elevated and the $t_{1/2}$ was prolonged after administration of IV nicardipine 0.6 mg/h for 24 hours.[2,56]

After administration of IV nicardipine, mean plasma clearance (CL) was lower in patients with mild to moderate hypertension and impaired renal function (mean creatinine clearance [CL_{CR}] 2.3 L/h [39 mL/min]) than in patients with mild to moderate hypertension and normal renal function (CL_{CR} 5.5 L/h [91 mL/min]) [6.53 vs 10.41 mL/min/kg; $p < 0.05$].[57] AUC was also elevated in patients with renal impairment.[2,57] In dialysis patients, mean plasma CL was not significantly different from that of hypertensive patients with normal renal function.[57]

The steady-state pharmacokinetics of nicardipine were similar in young healthy adult patients and elderly hypertensive patients (aged >65 years).[2]

3.4 Drug Interactions

Cimetidine increases nicardipine plasma concentrations after oral administration;[2] however, the disposition of a 12-hour IV infusion of nicardipine 2 mg/h was unaffected by multiple bolus injections of cimetidine 300mg every 6 hours for 48 hours in healthy volunteers (data from an abstract).[58]

The disposition of ciclosporin is altered by concomitant oral nicardipine, with increases of 10–31% in ciclosporin plasma concentrations.[2,59] The manufacturer recommends careful monitoring of plasma ciclosporin concentrations during administration of IV nicardipine, with appropriate reductions in the dosage of IV nicardipine.[2]

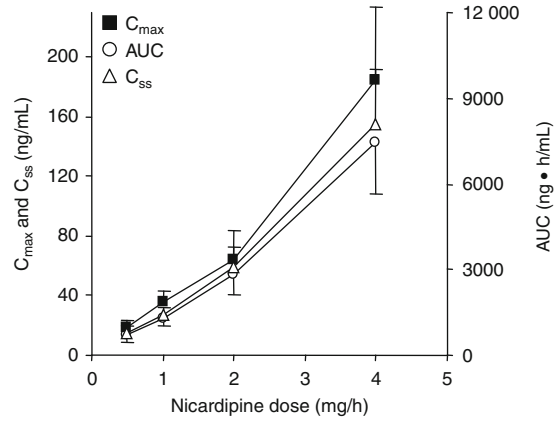

Fig. 1. The pharmacokinetics of intravenous nicardipine. Mean maximum (C_{max}) and steady-state (C_{ss}) plasma concentration and area under the plasma concentration-time curve (AUC) values from a randomised, double-blind, placebo-controlled trial in 37 patients with mild to moderate hypertension receiving a continuous intravenous infusion of nicardipine for 48 hours at doses of 0.5, 1.0, 2.0 and 4.0 mg/h.[17] C_{max}, C_{ss} and AUC were calculated from a noncompartmental model.

Use of some inhalational anaesthetics (sevoflurane, enflurane, isoflurane) may alter the pharmacokinetics of nicardipine.[60] Nicardipine C_{max} was higher when administered during sevoflurane anaethesia than during enflurane or isoflurane anaesthesia (39.8 vs 28.3 and 32.6 ng/mL; $p < 0.05$). The elimination half-lives of enflurane and sevoflurane were longer than that of isoflurane ($t_{1/2}$ 28 and 29 vs 14 minutes; $p < 0.05$).

Concomitant administration of a continuous infusion of nicardipine 2 μg/kg/min and vecuronium 1.5 μg/kg/min reduced the total plasma clearance of vecuronium (2.90 mL/kg/min with IV nicardipine vs 3.9 mL/kg/min without IV nicardipine; $p < 0.05$) in anaesthetised patients undergoing otolaryngeal surgery.[61]

4. Therapeutic Efficacy

4.1 Severe Hypertension

The efficacy of IV nicardipine in lowering BP in patients with severe hypertension (n = 40–123) has been investigated in randomised trials (focus of this section; see table III).[62-65] Severe hypertension was defined as systolic BP (SBP) >200mm Hg and diastolic BP (DBP) >120mm Hg,[62,64] DBP >115mm Hg,[63] or SBP >160mm Hg and DBP >100mm Hg accompanied by cardiovascular abnormalities and acute pulmonary oedema.[65] The mean age of patients was 52–67 years. Patients with a history of stroke or myocardial infarction were excluded from the trials. IV nicardipine or the comparator was titrated to achieve therapeutic BP target levels (see table III for further details). The main endpoints in these studies were the number of patients achieving the target BP, the time to reach the target BP, the dosages at which target BP was reached and the changes from baseline in SBP and DBP.

IV nicardipine is an effective agent for rapidly lowering BP in patients with severe hypertension with and without end-organ damage.[62-65]

A continuous infusion of IV nicardipine (maximum 15 mg/h) exerted a prompt hypotensive effect in a double-blind, placebo-controlled, multicentre

Table III. Comparative trials of intravenous (IV) nicardipine (NIC) in patients (pts) with severe hypertension (SBP >200mm Hg and DBP >120mm Hg[62,64] or SBP >160mm Hg and DBP >100mm Hg accompanied by cardiovascular abnormalities and acute pulmonary oedema[65]). IV NIC or the comparator was titrated to achieve therapeutic blood pressure (BP) target levels, with a maintenance dose administered for up to 12 hours in two of the studies[62,64]

Study	Study design	Treatment	No. of pts	Mean baseline BP (mm Hg)	Pts achieving therapeutic BP target[a] (%)	Time to therapeutic target (min)	Dosage required to achieve therapeutic target	Mean no. of dose adjustments per hour
Comparison with PL								
Wallin et al.[62]	r, db, mc	IV NIC[b]	73	213/126	91*	77	8.7 mg/h	
		PL[c]	50	216/125	0			
Comparisons with NP								
Neutel et al.[64]	r, ol, mc	IV NIC[b]	61	217/128	98	62	7.8 mg/h	1.7†
		IV NP[d]	60	219/128	93	63	1.8 μg/kg/min	3.3
Yang et al.[65]	r, ol, sc	IV NIC[e]	20	196/114	NR	<60	3.5 μg/kg/min	
		IV NP[e]	20	195/115	NR	<60	1.5 μg/kg/min	

a SBP ≤160mm Hg[62,64] and DBP ≤95mm Hg[62,64] or a decrease in DBP ≥25mm Hg[62,64] or a decrease in SBP ≥50mm Hg,[64] or BP at 80% of initial MAP.[65]

b Initiated at 5 mg/h and then titrated to a maximum of 15 mg/h.

c If pts did not achieve a titration response (SBP ≤180mm Hg or a SBP reduction of ≥20mm Hg; DBP ≤110mm Hg or a decrease in DBP ≥15mm Hg) within 1 hour, the trial was opened and pts were treated with alternative antihypertensive agents or ol IV NIC.

d Initiated at <0.5 μg/kg/min and then titrated to a maximum dose of 10 μg/kg/min.

e NIC initiated at 3 μg/kg/min and NP initiated at 1 μg/kg/min and then both agents were titrated to achieve target BP.

db = double-blind; **DBP** = diastolic blood pressure; **MAP** = mean arterial pressure; **mc** = multicentre; **NP** = nitroprusside; **NR** = not reported; **ol** = open-label; **r** = randomised; **PL** = placebo; **SBP** = systolic blood pressure; **sc** = single-centre; * $p < 0.001$ vs PL; † $p < 0.05$ vs comparator.

trial in 123 patients with severe hypertension (table III).[62] End-organ damage was present in 72 of the patients. At the end of the double-blind phase of the trial, the therapeutic target was achieved in significantly more IV nicardipine than placebo recipients (91% vs 0%; $p < 0.001$) [table III]. The time to reach the target BP level was 77 minutes. Of the placebo patients who did not respond during the blinded phase of the trial, subsequent open-label treatment with IV nicardipine resulted in 44 of 49 patients achieving the therapeutic target.[62] Patients with and without end-organ damage responded equally to IV nicardipine treatment.

Administration of IV nicardipine by bolus (2mg) and then constant infusion for 24 hours (initiated at 2 mg/h and titrated to a maximum of 30 mg/h; maintenance dose 2.0–15.5 mg/h) was as effective as administration of IV nicardipine by constant infusion alone for 24 hours (titrated from 2 mg/h to a maximum of 30 mg/h; maintenance dose 2.0–15.4 mg/h) in a randomised, double-blind study in 53 patients with severe hypertension.[63] Both regimens achieved the therapeutic target (20 and 10mm Hg reduction in SBP and DBP) within 5–10 minutes.

In open-label trials (n = 40[65] and 121[64]), IV nicardipine was as effective as IV nitroprusside in the reduction of BP in patients with severe hypertension (table III). In the smaller trial, a therapeutic response was achieved in <60 minutes with both IV nicardipine and nitroprusside.[65] In the larger trial, a similar proportion of patients (≥93%) achieved the therapeutic BP target within a similar timeframe (approximately 60 minutes), when treated with a continuous IV infusion of nicardipine or nitroprusside (table III).[64] The mean decrease in SBP and DBP was not significantly different between the two treatment groups. The mean decreases in SBP and DBP were 61 and 40mm Hg after 4 hours of IV nicardipine and 59 and 38mm Hg after 4 hours of IV nitroprusside.[64] However, hypotension (BP <100/50mm Hg) was reported in significantly fewer patients treated with IV nicardipine than with IV nitroprusside (2 vs 10 patients; $p < 0.05$). The mean increases in heart rate were similar in both treatment groups (12 and 10 beats/min). The mean number of adjustments per hour required to reach the therapeutic target were significantly lower with IV nicardipine than with IV nitroprusside (table III).

4.2 Perioperative Use

4.2.1 Postoperative Hypertension

This section focuses on data from randomised trials that compared IV nicardipine with placebo[66] or IV nitroprusside[67-69] in patients (n >50) with postoperative hypertension who had undergone either cardiac or noncardiac surgery (see table IV for further details of study design). The efficacy of IV nicardipine in controlling postoperative hypertension after neurosurgery is reviewed in section 4.3.

IV nicardipine was administered as an infusion or bolus dose followed by an infusion, with drug titration occurring until the therapeutic response was achieved (see table IV for details). Postoperative hypertension was defined as SBP ≥140mm Hg or DBP ≥95mm Hg,[66,68,70] Mean arterial pressure (MAP) ≥100mm in the immediate postoperative period (up to 3–6 hours after surgery),[67] or BP >15% above baseline value or if limits established by the vascular surgeon were exceeded.[69] The mean age of the patients was 62–70 years. The main endpoints of these studies are reported in table IV.

IV nicardipine rapidly and effectively controlled postoperative hypertension in patients who had undergone either cardiac or noncardiac surgery.

In a double-blind trial in 122 patients who had undergone cardiac and noncardiac surgery, a therapeutic response (a ≥15% reduction in SBP or DBP from baseline) was rapidly (10–12 minutes) achieved in significantly more patients treated with IV nicardipine than with placebo (table IV); the mean infusion rate to achieve the therapeutic response was 12.8 mg/h.[66] The magnitude of the reduction in BP was similar in both cardiac and noncardiac postsurgical patients. Heart rate increased by 5 beats/min in recipients of IV nicardipine and decreased by 8 beats/min in recipients of placebo ($p < 0.05$). During a maintenance infusion period of 6.8 hours, BP was sustained with minimal dose adjustments of IV nicardipine (mean infusion rate 3.0 mg/h). According to a subanalysis

Table IV. Use of intravenous (IV) nicardipine (NIC) in patients (pts) with postoperative hypertension (SBP ≥140mm Hg or DBP ≥95mm Hg,[66,68] mean arterial pressure (MAP) ≥100mm Hg,[67] or blood pressuer (BP) >15% above baseline value or if limits established by the vascular surgeon were exceeded[69])

Study	Surgery	Study design	Treatment (duration; h)	No. of pts	Pts achieving therapeutic response (%)[a]	Mean time to response (min)	Mean infusion rate to achieve therapeutic response	Mean no. of adjustments required to achieve therapeutic targets
Comparison with PL								
IV Nicardipine Study Group[66]	Cardiac or noncardiac	r, db, mc	IV NIC (<8)[b,c,d]	71	94*	11.5	12.8 mg/h	
			PL (<8)[d]	51	12			
Comparisons with NP								
David et al.[67]	CABG	r, ol, mc	IV NIC (18–24)[e]	38	92[f]	25.9†	18.8 mg/h	
			IV NP (18–24)[g]	38	81[f]	35.4	1.43 μg/kg/min	
Dorman et al.[69]	Carotid endarterectomy	r, db, mc	IV NIC (<6)[h]	29	83†[i]			
			IV NP (<6)[g]	30	23[j]			
Halpern et al.[68]	Cardiac or noncardiac	r, ol, mc	IV NIC (<5)[b,c,d]	71	86	14.0††	13.3[j] and 13.9[k] mg/h	1.5†[j] and 1.6[k]
			IV NP (<5)[g]	68	88	30.4	2.4[j] and 1.5[k] μg/kg/min	5.1[j] and 4.6[k]

a A therapeutic response was defined as a ≥15% reduction from baseline in SBP or DBP,[66,68] MAP reduced to 85mm Hg within 50 min of initial hypertension episode,[67] or not clearly stated.[69]

b 10 mg/h for 5 min, then 12.5 mg/h for 5 min, then 15.0 mg/h for up to 15 min.

c Once the therapeutic target was reached, pts entered an 8-hour maintenance phase during which they received IV NIC 3 mg/h titrated to maintain BP control.

d If pts did not achieve a therapeutic response during titration, the trial was opened and pts were treated with alternative antihypertensive agents or ol IV NIC.

e 2.5mg bolus infused over 5 min and repeated every 10 min until a maximal dose of 12.5mg; then 2–4 mg/h.

f Primary endpoint.

g 0.5 μg/kg/min increased to 1, 2, 4 and 6 μg/kg/min at 10-min intervals;[67] 0.125 μg/kg/min increased by 0.125–0.375 μg/kg/min every 3–5 min;[69] or 0.5 μg/kg/min increased by 0.5–1.5 μg/kg/min at 5-min intervals (maximum dose 10 μg/kg/min for 10 min)[68] until therapeutic targets were reached.

h 2.5mg bolus and then 3 mg/h.

i During the first 10 min.

j Cardiac surgery.

k Noncardiac surgery.

CABG = coronary artery bypass graft; **db** = double-blind; **DBP** = diastolic blood pressure; **mc** = multicentre; **NP** = nitroprusside; **ol** = open label; **PL** = placebo; **r** = randomised; **SBP** = systolic blood pressure; * $p < 0.001$ vs PL; † $p \leq 0.05$, †† $p < 0.01$ vs IV NP.

of patients who had undergone head and neck surgery, a therapeutic response occurred in five of the six IV nicardipine recipients (83%) and in two of the nine placebo recipients (22%) [$p < 0.002$].[70]

A continuous infusion of IV nicardipine was at least as effective as a continuous infusion of IV nitroprusside in the reduction of postoperative hypertension following noncardiac surgery[68,69] (including carotid endarterectomy[69]) or cardiac surgery[67,68] (including coronary artery bypass graft [CABG] surgery[67]) [table IV]. In two of the studies,[67,68] therapeutic response was achieved in a similar number of recipients of IV nicardipine or IV nitroprusside, but the time to reach a therapeutic response was shorter with IV nicardipine ($p < 0.01$; table IV). In the largest study in a subgroup of those undergoing cardiac surgery, fewer dosage adjustments were required with IV nicardipine to achieve the therapeutic target (1.5 vs 5.1; $p \leq 0.05$).[68] In the study in patients undergoing CABG,[67] increases in heart rate (3% vs 17%; $p < 0.001$) and decreases in mean pulmonary artery pressure (5% vs 19%; $p <$

0.05) were significantly less with IV nicardipine than IV nitroprusside. IV nicardipine (bolus dose and then continuous infusion; see table IV for further dosage details) achieved therapeutic control in a greater proportion of patients within the first 10 minutes (83% vs 23%; $p < 0.01$) in the study in patients undergoing carotid endarterectomy.[69]

4.2.2 Intra-operative Haemostability

The efficacy of IV nicardipine in maintaining intra-operative haemostability during anaesthesia has been assessed in preliminary studies in patients undergoing cardiac and various other surgical procedures; see section 4.3.4 for a specific review of the use of IV nicardipine during neurovascular surgery.

Cardiac Surgery

IV nicardipine administered as a bolus dose or as a continuous infusion was effective in the short-term reduction of BP and in the prevention of myocardial ischaemia during anaesthesia in patients undergoing cardiac surgery.[53,71,72]

In a randomised, double-blind, dose-ranging study in 40 anaesthetised patients undergoing cardiac surgery,[53] a bolus dose of IV nicardipine dose-dependently lowered SBP, DBP and MAP. Maximum decreases in MAP were 15, 21, 24 and 30mm Hg ($p < 0.01$) after administration of a bolus dose of IV nicardipine 0.25, 0.5, 1 and 2.0mg, respectively. The mean time to maximum response was rapid (66, 63, 56 and 101 seconds, respectively) and recovery to half maximum response occurred within 3–7 minutes, without changes in heart rate. IV nicardipine had no effects on ventricular preload or cardiac output. The authors of the study hypothesised that the attenuation of reflex sympathetic activity by general anaesthesia may explain the absence of reflex tachycardia or increased cardiac output after nicardipine administration.[53]

An intraoperative continuous infusion of IV nicardipine in anaesthetised patients undergoing CABG procedures (n = 77[71] and 120[72]) significantly reduced MAP and demonstrated anti-ischaemic effects in randomised, open-label, comparative trials.[71,72]

In one of these trials,[71] the duration of myocardial ischaemic episodes (ST-segment elevation or depression of at least 1mm, assessed using a two-channel Holter monitor) during the intraoperative post-bypass period was significantly shorter with IV nicardipine 0.7–1.4 μg/kg/min (3.2 min/h; $p \leq 0.05$), but not IV nitroglycerin 0.5–1.0 μg/kg/min (8.2 min/h), than with placebo (17.2 min/h). Myocardial episodes with ST-segment elevation or depression of at least 2mm were eliminated in recipients of IV nicardipine ($p \leq 0.05$ vs placebo), but not in recipients of nitroglycerin (0.3 episodes/h) or placebo (0.17 episodes/h). In the other study,[72] IV nicardipine (initial rate of 3 μg/kg/min) and IV nitroprusside (initial rate of 1 μg/kg/min) were both effective in controlling MAP, with heart rate, cardiac index and rate-pressure increasing compared with baseline after sternotomy, but systemic vascular resistance remaining low. Ischaemic changes (assessed on the electrocardiogram) occurred in 28% of patients in the control group (who received no vasodilator), 25% of patients treated with IV nitroprusside and 10% of patients treated with IV nicardipine.

Other Surgical Procedures

IV nicardipine provided effective, long-lasting treatment for intraoperative hypertension in patients undergoing abdominal surgery when administered as a 5mg bolus dose in a small, randomised, double-blind, placebo-controlled study.[73] Patients had MAP >110mm Hg 5 minutes after an additional injection of fentanyl 4 g/kg. If MAP had not decreased by at least 10% at 15 minutes, the trial was opened and patients received IV nicardipine 5mg. None of the ten patients randomised to nicardipine required additional nicardipine in an open-label manner; in contrast, seven of the ten patients in the placebo group required open-label nicardipine. IV nicardipine reduced SBP, DBP and MAP by 34% during treatment. In nicardipine recipients, MAP remained below pre-nicardipine injection values and near preoperative values for 45 minutes. There were no reports of severe hypotension in IV nicardipine recipients, although the nicardipine injection was stopped at 3mg in two patients because of the rate of pressure reduction.

IV nicardipine or IV nitroglycerin both administered as continuous infusions at a dosage of 1–4 μg/

kg/min controlled perioperative hypertension in 40 patients receiving anaesthesia (study design not stated).[74] Patients were undergoing cardiothoracic, orthopaedic or general surgery and had a history of hypertensive episodes during anaesthesia, and/or a history of SBP >160mm Hg and/ or DBP >95mm Hg.[74] Nicardipine and nitroglycerin were titrated to achieve a target SBP at 70% of pretreatment levels or a MAP of 70–90mm Hg; dosages were then maintained during anaesthesia and for 2 hours after the operation. IV nicardipine controlled BP more rapidly than nitroglycerin (10.5 vs 18.7 minutes; $p < 0.05$), with fewer dosage adjustments need to achieve a therapeutic response (2.5 vs 6.2; $p < 0.05$) and fewer patients having a hypotensive episode (5% vs 30%; $p < 0.05$). The increase in heart rate at the end of the maintenance phase was significantly lower with IV nicardipine than IV nitroglycerin (8% vs 30%; $p < 0.05$).

4.2.3 Controlled Intra-operative Hypotension

This section focuses on data from randomised, open-label studies in anaesthetised patients (including adolescents[75,76]) undergoing surgical procedures (table V).[75-78] Patients with hypertension, coronary diseases, cerebrovascular diseases, hepatic or renal insufficiency were excluded from the trials.[76-78] The main endpoints assessed in these trials are reported in table V.

IV nicardipine was effective in inducing deliberate hypotension (MAP 50–65mm Hg), and consequently limiting blood loss during specified surgical procedures (spine[75,76,78] or hip[77]).

In small (n = 20–49) studies in patients undergoing spinal or hip surgery,[75-78] IV nicardipine and IV nitroprusside achieved sustained and controlled hypotension throughout the operation with blood loss (table V) and transfusion rates being generally similar in both treatment groups. There was no change in pulmonary capillary wedge pressure during the nicardipine-induced hypotensive period.[77,78] Once the infusion had ceased, the time to reach baseline MAP was longer with IV nicardipine than with IV nitroprusside (table V).

4.2.4 Prior to Laryngoscopy and Tracheal Intubation

This section focuses on data from randomised, double-blind, placebo-controlled studies in normotensive (n = 45–106)[79-82] or hypertensive (n = 37)[83] patients enrolled for elective surgery who had undergone induction anaesthesia (table

Table V. The use of intravenous (IV) nicardipine (NIC) to achieve controlled hypotension (mean arterial pressure [MAP] 50–65mm Hg) in patients (pts) undergoing surgical procedures. In randomised, open-label trials, pts were treated with a continuous infusion of IV NIC or IV nitroprusside (NP)

Study	Treatment (duration; min)	No. of pts	Time to achieve hypotension (min)	Blood loss (mL)	Time to restoration of baseline MAP after infusion (min)
Spinal surgery					
Bernard et al.[78]	IV NIC (270)[a]	10	9	5120[b]	43
	IV NP (230)[c]	10	11	6170[b]	20
Hersey et al.[75][d]	IV NIC (264)[a]	10	5–10	761	26.8
	IV NP (264[c]	10	5–10	1297.5	7.3†
Lustik et al.[76][d]	IV NIC (342)[e]	24	21*	1129	66.5
	IV NP (334)[c]	25	8	960	20††
Hip arthroplasty					
Bernard et al.[77]	IV NIC (89)[a]	12	7	415	
	IV NP (87)[c]	12	7	428	

a Initiated at 10 μg/kg/min and continued until target MAP was reached, and then decreased to 1 μg/kg/min and titrated as required.

b Sponges plus suction.

c Initiated at 0.5[76] or 1[75,77,78] μg/kg/min, and then titrated until target MAP was reached.

d Adolescent pts undergoing idiopathic scoliosis repair; mean age 14 years.

e Initiated at 5 mg/h, then increased by 2.5 mg/h every 5 min until target MAP was reached.

* $p < 0.001$ vs NP; † $p < 0.01$, †† $p < 0.001$ vs NIC.

VI). A bolus dose of IV nicardipine was administered 1,[80,83] 2[79] or 3[81,82] minutes prior to the start of laryngoscopy.

Bolus doses of IV nicardipine attenuated the hypertensive responses to laryngoscopy and tracheal intubation in normotensive or hypertensive surgery patients who had undergone induction anaesthesia.

In a dose-ranging study in 106 normotensive patients who had received a standardised anaesthetic induction sequence, bolus IV nicardipine 0.5–4mg administered before laryngoscopy decreased MAP in a dose-dependent manner.[79] MAP increased in all groups after intubation; however, the peak MAP value after intubation was not significantly different to baseline values in recipients of a bolus dose of IV nicardipine 1mg (1% between-group difference).[79]

Similar results were obtained in comparative trials in normotensive[80-82] or hypertensive[83] patients who had undergone anaesthetic induction (table VI). A bolus dose of IV nicardipine 0.03 mg/kg significantly attenuated the increase in SBP,[80-82] DBP[80,82] or MAP[82,83] associated with laryngoscopy and tracheal intubation, in a manner similar to that with other calcium-channel antagonists (verapamil,[80,82] diltiazem[80,83]) [table VI], but did not control post-intubation tachycardia (table VI).[80-83] In the study in hypertensive patients,[83] the increase from baseline in heart rate with IV nicardipine was significantly greater than that with diltiazem ($p < 0.05$). Tachycardia was not effectively controlled by the addition of IV esmolol 0.5 or 1.0 mg/kg to a bolus dose of IV nicardipine 0.015 or 0.03 mg/kg in a study in normotensive patients (table VI).[81]

4.2.5 Prior to Emergence from Anaesthesia and Extubation

IV nicardipine was effective in attenuating increases in BP during anaesthesia emergence and tracheal extubation, according to data from a randomised, double-blind, placebo-controlled trial in 45 anaesthetised patients undergoing surgery (American Society of Anesthesiology class I–II).[84] Patients were aged >18 years. IV nicardipine 0.015 or 0.03 mg/kg was administered 2 minutes after muscle relaxant reversal. Haemodynamic parameters were assessed over the next 15 minutes.

The greatest and most consistent control of BP occurred in recipients of IV nicardipine 0.03 mg/kg. The difference in MAP between recipients of IV nicardipine 0.03 mg/kg and placebo was significant from 1–8 minutes after drug administration; the greatest decrease in MAP (from 93mm Hg at baseline to 75mm Hg) occurred after 3 minutes. No episodes of hypotension were reported. However, there was an increase in heart rate in both nicardipine groups at the time of extubation.

4.3 Neurovascular Indications

4.3.1 Aneurysmal Subarachnoid Haemorrhage

This section focuses on data from two large (n = 365[37] and 906[38,39]), randomised, double-blind, multicentre trials (table VII) in patients with recent aneurysmal subarachnoid haemorrhage treated with IV nicardipine. [37-39] Data from one of these trials (n = 906) was presented in two publications[38,39] (one publication presented angiographic and transcranial Doppler ultrasound data from 235 patients[39]). The primary endpoint in this trial was the percentage of patients achieving a good recovery according to the Glasgow Outcome Scale at 3 months.[38]

Patients in both trials were aged >18 years. Aneurysmal subarachnoid haemorrhage was diagnosed by patient medical history and confirmed by computerised tomography or lumbar puncture, with angiography confirming a saccular aneurysm. [38] In both trials, the incidence and severity of vasospasm was determined angiographically on days 7–11 following the subarachnoid haemorrhage.

IV nicardipine had similar clinical outcomes at 3 months to treatment with placebo (table VII).[37-39] Nevertheless, evidence of the ability of IV nicardipine to prevent cerebral vasospasm was observed in the two trials. In the placebo-controlled trial,[38,39] a continuous IV infusion of nicardipine 2.5 μg/kg/min for up to 14 days was associated with a significantly reduced incidence of symptomatic and angiographic evidence of vasospasm compared with placebo (table VII), and a reduced need for prophylactic intentional hypervolaemic/induced hypertension (294 fewer treatment days per 1000 patients occurring with IV nicardipine treatment; $p <$

Table VI. Maintenance of haemodynamic stability by intravenous (IV) nicardipine (NIC) during laryngoscopy and tracheal intubation. In randomised, double-blind trials, patients (pts) who had undergone anaesthetic induction received a bolus dose of IV NIC or the comparator prior to laryngoscopy and tracheal intubation

Study	Bolus dose (mg/kg)[a]	No. of pts	Maximum change from baseline after intubation			
			SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	HR (beats/min)
Normotensive pts						
Mikawa et al.[80]	IV NIC 0.03[b]	15	↑5.0[c]	↑11.0[c]		↑34.0*[c]
	IV VER 0.1[b,d]	15	↑1.0[c]	↑5.0[c]		↑25[c]
	IV DIL 0.2[b]	15	↑7.0[c]	↑18.0*[c]		↑34*[c]
	PL	15	↑40*[c]	↑45.0*[c]		↑30*[c]
Tan et al.[81]	IV NIC 0.015 plus IV ESM 0.5[e]	20	↑*[c]	NR		↑*
	IV NIC 0.015 plus IV ESM 1.0[e]	20	↑*	NR		↑*
	IV NIC 0.03 plus IV ESM 0.5[e]	20	↑*	NR		↑*
	IV NIC 0.03 plus IV ESM 1.0[e]	20	NR	NR		↑*
	PL[e]	20	↑*	NR		↑*
Wig et al.[82]	IV NIC 0.03[e]	15	↓24.8**	↓14.5**		↑26*
	IV VER 0.1[e]	15	↓18.8**	↓12.73**		↑15.1*
	PL[e]	15	↑25.4**	↑23**		↑35.7**
Hypertensive pts (SBP >160mm Hg or DBP >95mm Hg)						
Fujii et al.[83]	IV NIC 0.03[f]	12			↑1†[g]	↑27*
	IV DIL 0.3[f]	12			↑2†[g]	↑12*†‡
	PL[f]	13			↑24*[g]	↑31*

a Administered 1[80,83] or 3[81,82] min prior to intubation, unless otherwise stated.

b Anaesthesia was induced with IV thiopental 4 mg/kg and IV fentanyl 2 μg/kg, followed by vecuronium 0.2 mg/kg, 2 min prior to laryngoscopy.

c Estimated from a graph.

d Administered 45 sec before the start of laryngoscopy.

e Administration of the study drug was followed 2 min later by IV thiopental 5 mg/kg,[81,82] IV fentanyl 1.5 μg/kg[81] and IV succinylcholine 1.5 mg/kg.[81,82] Laryngoscopy was initiated 30[82] or 60 sec[81] after the administration of IV succinylcholine.[81]

f Anaesthesia was induced by IV thiopental 5 mg/kg, followed by the administration of the study drug, and then IV succinylcholine 2 mg/kg and IV vecuronium 0.02 mg/kg. Laryngoscopy was initiated 1 min after the administration of IV succinylcholine.

g Immediately after intubation.

DBP = diastolic blood pressure; **DIL** = diltiazem; **ESM** = esmolol; **HR** = heart rate; **MAP** = mean arterial pressure; **NR** = not reported; **PL** = placebo; **SBP** = systolic blood pressure; **VER** verapamil; ↑ indicates increase; ↓ indicates decrease; * $p \leq 0.05$, ** $p < 0.001$ vs baseline; † $p < 0.05$ vs PL; ‡ $p < 0.05$ vs NIC.

0.05). The efficacy of a continuous infusion of a low dosage of IV nicardipine 1.25 μg/kg/min was similar to that of IV nicardipine 2.5 μg/kg/min (table VII); however, the lower dosage resulted in fewer adverse events (section 5).[37]

In addition, a small preliminary study in 18 patients (38 vessels) has investigated the efficacy of intra-arterial (IA) nicardipine for the treatment of vasospasm after aneurysmal subarachnoid haemorrhage.[35] Vasospasm was determined by serial clinical assessments and/or daily transcranial Doppler imaging and confirmed by angiography. IA nicardipine was administered at a dose of 0.5–6mg per vessel 4–14 days after vasospasm.

All vessels that were treated with IA nicardipine demonstrated angiographic improvement in the degree of vasospasm. Mean peak systolic velocities (assessed after transcranial Doppler imaging) were significantly reduced from baseline for 4 days after nicardipine infusion (268.9 vs 197.6 cm/sec; $p <$

0.001). Post-treatment neurological assessment (day of assessment not stated) indicated an improvement in 8 of 19 (42%) patients.[35]

4.3.2 Acute Intracerebral Haemorrhage

The efficacy of IV nicardipine in patients with acute intracerebral haemorrhage (ICH) was investigated in small, noncomparative studies.[44,85]

A continuous infusion of nicardipine initiated at 1 μg/kg/min and subsequently titrated was effective in maintaining BP 20–30% lower than that at baseline in 22 patients with acute ICH.[44] There was no change in middle cerebral arterial blood flow velocity, and cerebral perfusion pressure decreased at 24 and 72 hours, but was still >50mm Hg.

In another study in 29 patients with ICH (mean initial National Institutes of Health Stroke Scale [NIHSS] score 14),[85] IV nicardipine administered within 24 hours of symptom onset was effective in reducing and maintaining MAP <130mm Hg (without incurring adverse events that necessitated termination of therapy) [primary outcome] in 86% of the patients. Neurological deterioration (defined by a decline in Glascow Coma Scale from pretreatment values of ≥2 points, or an increase in NIHSS by ≥2 points) occurred in four patients and haematoma enlargement (increase in the volume of intraparenchymal haemorrhage of >33% as measured by image analysis on the 24-hour CT scan compared with the baseline CT scan) occurred in five patients. IV nicardipine was initiated at 5 mg/h and titrated at increments of 2.5 mg/h every 15 minutes to a maximum of 15 mg/h. At 1 month, favourable outcomes (defined as modified Rankin scale of ≤2) occurred in 38% of patients, with death occurring in 31% of patients.

4.3.3 Acute Ischaemic Stroke

The graded neurological exam score (100-point scale) improved from 41 at baseline to 63 at three months in a nonrandomised, open-label study in 43 patients (mean age 63 years) with acute ischaemic stroke treated within a mean 7 hours of onset of symptoms with a continuous infusion of IV nicardipine 3–7 mg/h for 72 hours.[86] Of the 20 patients who completed the 3-month assessment, 17 were improved, and no patients had a worsen condition. MAP decreased from 103mm Hg at baseline to 83mm Hg after 72 hours of infusion.

4.3.4 Neurovascular Surgery

Intracranial Aneurysm Clipping

IV nicardipine administered by continuous infusion at a dosage of 2.5 μg/kg/min[87] or as a bolus dose of 1mg[41] or 2mg[40] was effective in maintaining intra-operative haemostability during anaesthesia in patients undergoing intracranial aneurysm clipping, according to data from small, preliminary, open-label studies.

Table VII. Efficacy of intravenous (IV) nicardipine (NIC) in patients (pts) with recent aneurysmal subarachnoid haemorrhage.[a] In randomised, double-blind, multicentre trials, pts were treated with IV NIC or placebo (PL) for up to 14 days

Treatment (μg/kg/min)	No. of pts	Pts with symptomatic vasospasm (%)	Pts with angiographic moderate or severe vasospasm[b] (%) [total no. of pts assessed]	Mean MCA flow velocities >120 cm/sec[c] (% of pts) [total no. of pts assessed]	Overall outcomes assessed according to the Glasgow Outcome Scale at 3 months (% pts)	
					good recovery	death
Haley et al.[37]						
IV NIC 2.5	184	31	19 [44]	28	58[d]	11
IV NIC 1.25	181	31	39 [31]	40	59[d]	12
Haley et al.[38,39]						
IV NIC 2.5	449	32**	33* [112]	23** [112]	55	17
PL	457	46	51 [123]	49 [137]	56	18

a Diagnosed by pts' medical history and confirmed by CT or lumbar puncture; angiography demonstrated an aneurysm.

b Assessed on days 7–11 following haemorrhage by blinded investigators.

c Assessed by transcranial Doppler ultrasound.

d Primary endpoint.

MCA = middle cerebral artery; * $p < 0.01$, ** $p < 0.001$ vs PL.

In the largest study in 26 patients,[41] a bolus dose of IV nicardipine 2mg was as effective as a bolus dose of diltiazem 5mg in rapidly lowering MAP (a decrease in MAP of 32% and 33%; both $p < 0.01$ vs baseline). The blood flow velocity of the internal carotid artery was significantly increased in nicardipine recipients (from 34.2 to 40.6 cm/sec; $p < 0.01$), but not in recipients of diltiazem. Local cerebral blood flow was also increased with IV nicardipine (from 41.2 to 47.0 mL/100g/min; $p < 0.05$), but not with diltiazem. Similarly in another study (patient number not clearly stated), a bolus dose of IV nicardipine reduced MAP by 30% ($p < 0.01$ vs baseline), with maximum effects occurring 2 minutes after administration.[41] In a study in 24 patients, a continuous infusion of IV nicardipine commenced immediately after angiographic evidence of an intracranial aneurysm resulted in lower MAP prior to induction of anaesthesia than in the control group (86 vs 99mm Hg; $p < 0.05$) After intubation, MAP remained unchanged from pre-induction values in nicardipine recipients, but was reduced in the control group.[87]

Prevention of Post-operative Hypertension

IV nicardipine was an effective alternative to labetalol in controlling emergent hypertension during craniotomy. In a randomised, open-label study in 42 patients who had undergone craniotomy for tumour surgery, IV enalaprilat 1.25mg at dural closure was followed by bolus doses of IV nicardipine 2mg or IV labetalol 5mg administered as required to maintain SBP <140mm Hg.[88] The combination of enalaprilat plus labetalol or enalaprilat plus nicardipine was 99% and 90% effective in the control of SBP, with treatment failure (SBP >140mm Hg lasting for >2 minutes) occurring more frequently with nicardipine than labetalol (10 vs 4 episodes; $p = 0.05$).[88]

4.3.5 Severe Head Injury

IV nicardipine reversed the rise in Doppler flow velocity (DFV) in patients with severe head injury (Glasgow Coma Score ≤8; DFV ≥100 cm/sec for 6 hours) in a small (n = 30), randomised, double-blind, placebo-controlled study.[34] DFV was reduced below 100 cm/sec for 6 hours (primary endpoint) in 84% of nicardipine recipients compared with 27% of placebo recipients ($p < 0.001$). However, there was no between-group difference in the clinical outcomes of patients at 3 months. IV nicardipine was administered for 24 hours, at an initial dosage of 2.5 mg/h, with increases of 2.5 mg/h at 2-hourly intervals to a maximum infusion rate of 7.5 mg/h. The researchers recommended investigating the effects of IV nicardipine given over a longer period and before the onset of high DFV in a study with a greater number of patients.

4.4 Pre-Eclampsia

A limited number of prospective, noncomparative studies (n = 20–27) indicated that IV nicardipine is effective in rapidly managing hypertension in pregnant women with severe pre-eclampsia (DBP >110mm Hg[89-91] and proteinuria ≥0.3[89] or 0.5[91] g/L in a 24-hour urine collection).[89-91]

In a study in early-onset (median gestational age 27 weeks) pre-eclampsia patients who had not responded to treatment with other antihypertensive drugs, IV nicardipine achieved therapeutic targets (DBP <100mm Hg or <90mm Hg in patients with the syndrome comprising haemolysis, elevated liver enzymes and low-platelet counts) within a median of 23 minutes.[89] IV nicardipine was initiated at a dosage of 3 mg/h and subsequently titrated; treatment was continued until maternal and/or fetal condition warranted delivery. Delivery was postponed by a median 4.7 days (maximum dosage range 3–9 mg/h).

In another study in 20 patients with severe pre-eclampsia, IV nicardipine 2, 4 or 6 mg/h (mean duration of treatment 5 days) reduced DBP to <90 mm Hg in all patients after 72, 124 and 130 minutes[91] Similarly, in the other study in 20 patients,[90] IV nicardipine 1 μg/kg/min was effective in reducing MAP by 15–30% within 15–20 minutes in all patients. Once MAP was reduced by at least 15%, the dosage was reduced by 33% and the final dosage was adjusted to maintain MAP at 20–30% below the initial value. IV nicardipine was associated with an increase in heart rate that was significantly different from baseline after 35 minutes. The increase in heart

rate necessitated a reduction in nicardipine dosage in one patient. [90] Four patients were delivered within 1 hour of initiation of nicardipine therapy, and all infants did well at birth. All but one of the remaining patients switched to oral nicardipine after 1 day.

4.5 Aortic Dissection

IV nicardipine was effective in controlling BP in 31 patients with acute aortic dissection in an open-label trial.[92] The primary endpoint was the mean BP reduction on the third day after drug administration. IV nicardipine was initiated at an infusion rate of approximately 2 mg/h and titrated (maximum approximately 30 mg/h) until the therapeutic target (SBP 120–140mm Hg) was reached. The mean time to reach this target was 25.6 minutes, with an average IV nicardipine infusion rate of 2.1 mg/h. On the third day of treatment, SBP, DBP and MAP (119, 69 and 86mm Hg, respectively) were significantly (all $p < 0.05$) reduced from baseline values (147, 82 and 104mm Hg, respectively). The extent of aortic dissection progressed in 2 patients and remained unchanged in 23 patients, with assessment of disease progression not possible in the remaining patients. There were no cases of aortic dissection cases that progressed to rupture.

4.6 Special Patient Populations

4.6.1 Paediatric Patients

The efficacy of IV nicardipine in reducing BP in paediatric and adolescent patients in the perioperative or intensive care settings has been investigated in preliminary small (n = 7–20) observational studies,[93-96] and small (n = 9–29) retrospective reviews of medical records.[97-99] The ability to achieve BP control in adolescents undergoing spinal surgery has also been investigated (section 4.2.3).[75] Effective starting doses of nicardipine were 0.5–5 μg/kg/min, with maintenance dosages of 1–4 μg/kg/min.

Patients were aged from 2 days to 18 years (including neonates; gestational age 28–36 weeks[94,95]). Hypertension resulted from a variety of underlying causes, including surgical procedures,[93,95,97,99] renal disease,[93,94,98] extracorporeal membrane oxygen support[98] or corticosteroid administration.[94,95]

IV nicardipine was effective in rapidly reducing BP in these studies.[93-99] For example, in the largest retrospective study in 29 children with severe hypertension (BP >99th percentile for age and sex),[98] an IV infusion of nicardipine was initiated at a dosage of 0.8 μg/kg/min and then titrated to achieve the target BP (95th percentile BP for the patient's age and sex). The mean maintenance dose was 1.8 μg/kg/min, with patients receiving IV nicardipine until therapy with oral antihypertensive agents could be initiated or resumed (mean duration of 90 hours). BP targets were achieved within a mean 2.7 hours of treatment initiation, with SBP being reduced by 16% and DBP being reduced by 23%. Heart rate was increased by 7%.

4.6.2 Elderly patients

Data from a prospective, open-label trial indicated the efficacy of IV nicardipine in 28 elderly hypertensive patients aged 71–93 years with SBP ≥180mm Hg and/or DBP ≥100mm Hg.[100] Administration of IV nicardipine (bolus doses of 1.25, 2.5 and then 5mg, with each dose titrated over 6 minutes) significantly decreased SBP by 30% and DBP by 28%.

4.7 Acute Heart Failure

Several preliminary open-label studies have investigated the effects of IV nicardipine on haemodynamic parameters in patients with acute heart failure (see table 1).[30,101-103] However, this section will focus on data from a randomised, double-blind, dose-ranging trial in 53 patients.[29]

In this study, IV nicardipine 1–3 μg/kg/min increased cardiac output and decreased diastolic pulmonary artery pressure.[29] At baseline, cardiac index was 2.2 L/min/m^2, diastolic pulmonary artery pressure was 26mm Hg and SBP was 141–149mm Hg. The cardiac index increased significantly (all $p < 0.01$) from baseline by 41%, 32% and 35% in the 2 hours of treatment with IV nicardipine 1, 2 and 3 μg/kg/min, respectively. Decreases in diastolic pulmonary artery pressure were 27%, 26% and 31% (all $p < 0.01$), respectively. The decreases

in SBP were 16%, 21% and 27% (all $p < 0.01$ vs baseline), respectively, with the reduction experienced by recipients of nicardipine 3 μg/kg/min being significantly greater than that in recipients of 1 μg/kg/min ($p < 0.05$).[29]

4.8 Premature Labour

Nicardipine was at least as effective as salbutamol (albuterol) in the management of patients presenting with premature labour and hypertension, according to data from a randomised, open-label study (n = 90).[104] In recipients of IV nicardipine initiated at 30 mL/h (3 mg/h) and then titrated to a maximum dose of 60 mL/h (6 mg/h), the term of delivery was 38.4 weeks compared with 37.6 weeks ($p < 0.05$) in recipients of IV salbutamol initiated at 30 mL/h (0.15 mg/h) and titrated to a maximum of 60 mL/h. The neonatal birthweight was similar in both groups (3131 vs 3019g), and there were no significant between-group differences in Apgar scores at 1 and 5 minutes, or in the number of neonates admitted to the premature infant unit. SBP and DBP were significantly ($p < 0.05$) reduced in the IV nicardipine, but not the salbutamol group, but there were no accompanying clinical signs of hypotension in nicardipine recipients.[104]

4.9 Raynaud's Phenomenon

Administration of IV nicardipine 5 mg/h over 85 minutes increased blood flow through forearm muscle by 41% and decreased forearm resistance by 26% in 12 patients with Raynaud's phenomenon in a randomised, double-blind, crossover, placebo-controlled study.[105] Finger skin temperature increased by 4.6°C from baseline values ($p < 0.001$) with IV nicardipine, but showed no change with placebo. After cold-induced vasoconstriction, the finger skin blood flow also had a better recovery with IV nicardipine than with placebo ($p < 0.001$).

4.10 Electroconvulsive Therapy

A bolus dose of IV nicardipine, when administered in combination with labetalol, was effective in the prevention of an acute haemodynamic response to electroconvulsive therapy (ECT), according to data from randomised, double-blind, crossover studies (focus of this section).[106,107]

In a dose-ranging study in 25 patients undergoing a series of four ECT treatments, a bolus dose of IV nicardipine 40 or 80 μg/kg, compared with placebo, administered immediately prior to ECT significantly attenuated the increase in MAP from baseline values after ECT (increases of 7% and 7% vs 30%; $p < 0.05$).[107] Moreover, with these doses of IV nicardipine, compared with placebo, a significantly lower dosage of supplemental labetalol was required than with placebo (7 and 5 vs 22mg; $p < 0.05$). The 40 μg/kg dose of nicardipine, compared with the 80 μg/kg dose, was associated with a lower heart rate (105 vs 125 beats/minute; $p < 0.05$) at the time of the ECT stimulus. Moreover, since a dose of IV nicardipine 80 μg/kg decreased MAP on awakening (91mm Hg) to lower than that at baseline (102mm Hg; $p < 0.05$), the researchers concluded that a bolus dose of IV nicardipine 40 μg/kg was optimal for use in ECT treatment. IV nicardipine had no effect on the duration of ECT-induced seizure activity.

IV nicardipine 2.5mg administered as a bolus dose in combination with IV labetalol 10mg, administered 4 minutes prior to induction of anaesthesia, was an effective regimen for preventing the acute haemodynamic response to ECT, according to data from an other study.[106] This combination was associated with a 20% decrease in MAP immediately prior to ECT and a MAP of 93mm Hg at discharge which was significantly lower than that at baseline (105mm Hg; $p < 0.05$).

5. Tolerability

IV nicardipine is generally well tolerated in patients requiring acute control of hypertension, with adverse events generally being non-serious and mostly the expected consequences of vasodilation.

Headache, hypotension, nausea, vomiting and tachycardia were the most commonly reported adverse events with IV nicardipine in two, double-blind, placebo-controlled, multicentre trials in patients requiring acute control of severe[62] or postoperative[66] hypertension. Combined analysis of the incidence of adverse events from these trials is

presented in figure 2 (data obtained from the manufacturer's prescribing information).[2] IV nicardipine was initiated at 5[62] or 10[66] mg/h and then titrated to achieve therapeutic BP targets (maximum dosage 15 mg/h). The presence of adverse events occasionally required adjustment of the dosage of IV nicardipine, with therapy being discontinued in approximately 12% of patients, mainly due to hypotension, headache and tachycardia.[2]

A continuous infusion of IV nicardipine 2.5 μg/kg/min for up to 14 days was generally well tolerated in a randomised, double-blind, placebo-controlled, multicentre trial in 906 patients with aneurysmal subarachnoid haemorrhage.[38] Hypotension (SBP <100mm Hg) was reported in 34.5% of IV nicardipine recipients and 17.5% of placebo recipients, with only 3% of patients in both groups reporting severe hypotension. In a trial of similar design in 365 patients with aneurysmal subarachnoid haemorrhage,[37] the incidence of hypotension was 33% with a continuous infusion of IV nicardipine 2.5 μg/kg/min and 28% with a dosage of 1.25 μg/kg/min. The incidence of renal dysfunction was also similar in both dosage groups (5% and 6%); however, pulmonary oedema was more common with high- than low-dosage nicardipine (34% vs 20%; $p < 0.01$).

IV nicardipine was generally better tolerated than IV nitroprusside in patients with severe[64] or postoperative[68] hypertension, according to data from two large (n = 139[68] and 121[64]), randomised, open-label, multicentre trials. In one of these trials (section 4.2.1 and table IV for further details of study design and drug dosages),[68] adverse events occurred in 18% of recipients of IV nitroprusside and 7% of recipients of IV nicardipine; the between-group difference was not significant. However, significantly more recipients of IV nitroprusside than recipients of IV nicardipine withdrew from the study (9% vs 0%; $p < 0.05$).[68] In the other trial (see section 4.1 and table III for further details of study design and drug dosages),[64] the incidence of adverse events was significantly higher in recipients of IV nitroprusside than IV nicardipine (56% vs 31%; $p < 0.05$). The percentage of patients with hypotension (16% vs 3%), dizziness (16% vs 3%), nausea (13% vs 7%) and vomiting (12% vs 2%) was significantly higher in recipients of IV nitroprusside than IV nicardipine (all $p < 0.05$). However, these results must be interpreted with caution given the open-label nature of the trials.

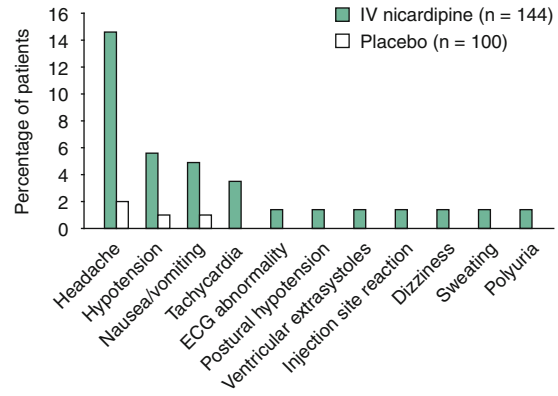

Fig. 2. Tolerability of a continuous infusion of intravenous (IV) nicardipine in patients with severe[62] or postoperative[66] hypertension enrolled in two randomised, double-blind, placebo-controlled, multicentre trials (data obtained from the manufacturer's prescribing information[2]). IV nicardipine was initiated at 5[62] or 10[66] mg/h and then titrated to achieve therapeutic blood pressure targets (maximum dosage 15 mg/h). Adverse events reported in ≥1% of patients are presented.

The tolerability of IV nicardipine in paediatric patients and pregnant women has not been established in well designed trials. However, in small, open-label studies[89-91,93-100] in these patients (section 4.4, 4.6 and 4.8), IV nicardipine was generally well tolerated, with tachycardia, hypotension and headache being the most commonly reported adverse events. In small studies where IV nicardipine was administered to patients with severe, early-onset pre-eclampsia, no deleterious effects of nicardipine therapy on the fetus or neonates were reported.[89-91] A change in IV nicardipine dosage or hypotension during IV nicardipine therapy did not result in an increase in deceleration in the fetus that required treatment.[89]

6. Dosage and Administration

IV nicardipine is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable. For prolonged control of

BP, patients should be transferred to oral medication as soon as their clinical condition permits.[2]

The manufacturer recommends that IV nicardipine should be administered by continuous infusion at a concentration of 0.1 mg/mL.[2] However, IV nicardipine was shown to be compatible and stable at concentrations up to 0.5 mg/mL in glass or polyvinyl chloride containers for 24 hours at controlled temperatures in solutions of 5% dextrose, 5% dextrose and sodium chloride 0.45%, 5% dextrose and 0.9% sodium chloride, 5% dextrose and potassium 40 mEq/L, sodium chloride 0.45% and sodium chloride 0.9%.[108]

For the gradual reduction of BP, IV nicardipine should be initiated at 50 mL/h (5 mg/h). If the target BP is not achieved, the dosage may be increased by 25 mL/h (2.5 mg/h) every 15 minutes up to a maximum of 150 mL/h (15.0 mg/h), until the target BP is achieved.

For the rapid reduction of BP, IV nicardipine should be initiated at 50 mL/h (5 mg/h). If the target BP is not achieved, the dosage may be increased by 25 mL/h (2.5 mg/h) every 5 minutes up to a maximum of 150 mL/h (15.0 mg/h), until the target BP is achieved. Once the target BP has been achieved, the infusion rate should be decreased to 30 mL/h (3 mg/h).

There was no significant difference in the antihypertensive effect of IV nicardipine in patients aged ≥65 years compared with that in other adult patients.[2] The efficacy and tolerability of IV nicardipine has not been established in patients aged <18 years.[2]

IV nicardipine is contraindicated in patients with advanced aortic stenosis; the reduction of DBP may worsen rather than improve myocardial oxygen balance in these patients.[2] IV nicardipine is also contraindicated in patients with known hypersensitivity to the drug.[2]

Hypotension has been reported during the concomitant use of a β-blocker and a calcium channel antagonist. Although such interactions have not been reported with IV nicardipine, an increased volume of circulating fluids may be required in the event of such interactions.[2]

Local prescribing information should be consulted for dosage reduction guidelines in patients experiencing toxicity, recommendations in special populations and precautions.

7. Place of Intravenous Nicardipine in the Short-Term Management of Hypertension and Various Other Indications

Hypertension is a common primary diagnosis in the US,[109] affecting ≥ 65 million people in that country.[110,111] A variety of oral medications are currently used in the long-term treatment of hypertensive patients, with thiazide diuretics being recommended as initial treatment, either alone or with other classes of drugs (including ACE inhibitors, angiotensin II receptor antagonists or calcium channel antagonists).[112] However, in special situations, such as in patients with acute elevations of BP or those undergoing surgery, the management of hypertension may require the rapid lowering of BP over a short period of time. Drugs that can be administered intravenously are recommended in these patients.[109] In addition, such agents should be capable of regulating BP in a controlled manner, avoiding the risks of sudden falls in BP and being associated with a minimal risk of adverse events (including hypotension). The preparation of the agent should be rapid and simple, and transfer from IV to oral therapy should be uncomplicated.

Currently, a number of agents are available for parenteral administration in situations requiring the short-term management of BP. These include several vasodilators (e.g. nicardipine, nitroprusside, fenoldopam, nitroglycerin, enalaprilat and hydralazine) and adrenoceptor antagonists (e.g. labetalol and esmolol).[109]

Nitroprusside has commonly been used to rapidly control BP. It has a rapid onset of action and brief duration of action, with a hypotensive effect occurring within seconds of initiation of infusion. Plasma concentrations of nitroprusside decrease rapidly on discontinuation of an infusion.[113] However, because of the need for invasive haemodynamic monitoring and the association of nitroprusside with cya-

nide toxicity, alternative agents for the short-term control of BP have been used. One such agent is IV labetalol which is administered as a continuous infusion or bolus injection and has a rapid onset of action. However, labetalol is contraindicated in patients with heart failure, atrioventricular block, asthma and chronic obstructive pulmonary disease.[113] Moreover, the half-life of labetalol is long (6–8 hours).[114] Nitroglycerin is often the agent of choice in patients with coronary ischaemia, while esmolol has been used to effectively manage intraoperative tachycardia.[109] Nicardipine is a dihydropyridine calcium channel antagonist, with greater selectivity for L-type calcium channels in vascular smooth muscle than cardiac muscle (section 2). It induces relatively rapid changes in BP, with minimal cardiac inotropic and no significant venodilatory action. Consequently, this agent, administered intravenously by bolus or continuous infusion, has been used in a variety of situations that require the short-term control of BP. When administered by continuous infusion, nicardipine is generally initiated at a dosage of 5 mg/h and up-titrated gradually to obtain the desired therapeutic target. Once a stable BP is reached, most patients do not require additional dosage alterations.[113]

IV nicardipine has demonstrated efficacy in the short-term management of severe hypertension, including hypertensive emergencies (severe hypertension complicated by impending or progressive target organ dysfunction) [section 4.1]. Moreover, a continuous infusion of IV nicardipine was as effective as a continuous infusion of IV nitroprusside in the reduction of BP in these patients, with a similar proportion of patients (≥93%) achieving therapeutic BP targets within a similar timeframe (approximately 60 minutes). The use of nicardipine in these patients is in line with recommendations of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[109] This committee recommends that hypertensive emergencies be treated with an appropriate agent (including nicardipine, nitroprusside, fenoldopam and labetalol) combined with continual monitoring of BP within an intensive care unit.[109] In patients with hypertensive emergencies, it is recommended that MAP be initially reduced by ≤25% (within minutes to 1 hour).[109] Then, if the patient is stable, the BP should be reduced to 160/100–110mm Hg within the next 2–6 hours. Excessive reductions in BP may precipitate renal, cerebral or coronary ischaemia and should be avoided.[109,115] Subsequently, over the next 24–48 hours, further reductions towards normal BP may be permitted if the level of BP reduction is well tolerated and the patient is clinically stable. IV nicardipine was stable at concentrations up to 0.5 mg/mL, which enables critically ill patients to be administered smaller volumes of the drug (section 6). However, with higher concentrations, local site reactions may require administration of the IV nicardipine through a central line.

Acute control of hypertension may also be required in the perioperative period, when alterations in BP and the rate, rhythm and contractility of the heart are commonly encountered as a result of the physiological response to stress.[116] Uncontrolled perioperative hypertension can result in various outcomes, including increased haemorrhage at the surgical site, bleeding from anastomoses, intracranial haemorrhage, myocardial infarction, decompensation, arrhythmias or renal failure.

Hypertension is common in the postoperative period and is related to increased sympathetic tone and vascular resistance, with pain and increased vascular volume also contributing. Drugs that are recommended for the postoperative period include nitroprusside, nicardipine and labetalol.[109] Postoperatively, IV nicardipine was as effective as IV nitroprusside in the control of hypertension in patients who had undergone both cardiac and noncardiac surgery (section 4.2.1). However, with IV nicardipine, compared with IV nitroprusside, the time (cardiac and noncardiac patients) and the number of dosage adjustments (cardiac patients) required to reach a therapeutic response were significantly less.

The hypertension and tachycardia that result from the instrumentation of the pharynx and tracheal intubation may have life-threatening consequences, especially in patients with cardiovascular or cerebrovascular disease. Various pharmacological

agents have been used to blunt these responses including local anaesthetics,[117] α- and β-adrenoceptor antagonists,[118] vasodilators[119] and opioids.[120] In randomised, double-blind studies (section 4.2.4), a bolus dose of IV nicardipine attenuated the hypertensive response, but not the increase in tachycardia, after laryngoscopy and tracheal intubation in anaesthetised patients enrolled for elective surgery. A preliminary study also indicated that IV nicardipine was effective in attenuating increases in BP during anaesthesia emergence and tracheal extubation (section 4.2.5).

During certain surgical procedures, it may be advantageous to maintain BP within a certain range. In this regard, an IV infusion of nicardipine was effective in inducing deliberate hypotension (MAP 55–60mm Hg), and consequently limiting blood loss during surgical procedures in which surgical haemostasis may be difficult (e.g. surgery involving the hip or spine) [section 4.2.3]. Once infusion had ceased, the time to recovery to baseline MAP was longer with IV nicardipine than with IV nitroprusside. Data from a number of preliminary studies support the intraoperative efficacy of IV nicardipine in the acute control of BP in patients undergoing various other surgical procedures (including cardiovascular, neurovascular and abdominal surgery; section 4.2.2). Given that nicardipine is a potent coronary vasodilator, and increases coronary blood supply and myocardial oxygen supply (table I), preliminary studies indicate its efficacy in controlling BP and lessening the severity of myocardial ischaemia in patients undergoing CABG (section 4.2.2). IV nicardipine was also effective in controlling hypertension in the postoperative period after CABG (table IV). The pharmacodynamic profile of IV nicardipine (table I) also suggests that there is potential for this agent to be used in treating coronary vasospasm in arterial grafts (particularly the radial artery during harvesting). Preliminary data suggest that IV nicardipine may be effective in patients with heart failure, increasing cardiac index and decreasing diastolic pulmonary artery pressure (section 4.7). However, large, adequately powered, randomised, double-blind trials are required to satisfactorily compare the efficacy and tolerability of IV nicardipine with other agents in these settings. In addition, preliminary studies have demonstrated intracoronary nicardipine may potentially prevent and reverse the no-reflow phenomenon that can occur during percutaneous coronary interventions.[28] Investigation of this agent in prospective, randomised studies as a therapeutic option in the cardiac catheterisation laboratory is warranted.

Since normal cerebral vasoconstriction is calcium dependent, calcium channel antagonists (including oral nimodipine and IV nicardipine) have been investigated as a means of improving outcomes in patients with subarachnoid haemorrhage. Although oral nimodipine is strongly recommended by the American Heart Association (AHA) [level of evidence I–II, grade A], evidence supporting the use of other calcium channel antagonists is variable (level of evidence I to V; grade C).[121] Two well designed trials investigated the use of IV nicardipine in the prevention of cerebral vasospasm in patients with recent aneurysmal subarachnoid haemorrhage. IV nicardipine, compared with placebo, significantly reduced the incidence of symptomatic and angiographic evidence of vasospasm; the need for prophylactic intentional hypervolaemia/induced hypertension was also reduced in IV nicardipine recipients (section 4.3.1). However, overall outcomes at 3 months in IV nicardipine recipients were similar to those in patients who received standard management. Researchers suggested that this may be due to the efficacy of the hypervolaemia/hypertensive therapy in reversing the ischaemic effects of vasospasm once they occurred. The high incidence of hypotension in IV nicardipine, versus placebo, recipients (35% vs 18%; p-value not stated) may also potentially have contributed to the lack of between-group difference in clinical outcomes.[38] A preliminary study in patients with aneurysmal haemorrhage indicated that treatment of vessels with angiographic evidence of vasospasm with intra-arterial nicardipine resulted in angiographic dilatation (section 4.3.1).[35] Post-treatment neurological assessment indicated an improvement in many patients. However, data are insufficient to determine if IA

nicardipine provides any long-term clinical benefits. Larger, adequately powered, long-term studies are required to establish the efficacy and tolerability of the use of nicardipine in this setting.

A reduction in BP in patients with intracerebral haemorrhage is thought to reduce the risk of bleeding from ruptured small arteries and arterioles. However, data supporting the efficacy and tolerability of reducing BP in patients with intracerebral haemorrhage is limited. A special writing group of the Stroke Council of the AHA concluded that treatment of patients with ICH was only supported by anecdotal case series (level V evidence) and could only be considered a grade C recommendation. The writing group recommended that MAP be maintained <130mm Hg in patients with a history of hypertension and that cerebral perfusion pressure was maintained >70mm Hg in patients with elevated intracranial pressure.[122] Further preliminary data investigating the efficacy and tolerability of antihypertensive therapy in patients with ICH have been provided by studies by Qureshi et al.[85,123] An initial small (n = 27) study by this research group in patients with ICH indicated that rates of neurological deterioration and haematoma expansion were low (7% and 9%) after treatment with an antihypertensive regimen (a combination of boluses of IV labetalol or IV hydralazine, followed by IV nitroprusside if required).[123] Nevertheless, the use of this regimen did not provide consistent reduction in BP among the patients. More effective and consistent reduction in BP was achieved when the same research group treated patients with ICH with IV nicardipine in another small preliminary study (section 4.3.2). Target MAP <130mm Hg (consistent with AHA recommendations[122]) was achieved and maintained in most patients; rates of neurological deterioration and haematoma enlargement were also low (section 4.3.2). Data from the multicentre Antihypertensive Treatment of Acute Cerebral Hemorrhage study (funded by the National Institutes of Neurological Diseases and Stroke) will provide further data regarding the efficacy and tolerability of IV nicardipine when administered within 6 hours of symptom onset in this patient group.[85]

Despite the prevalence of arterial hypertension following stroke, the treatment of BP in patients with acute ischaemic stroke is problematic and the recommended treatment is less aggressive than that for patients with ICH.[124,125] The consensus of the Stroke Council for the AHA is that antihypertensives should be withheld unless DBP is >120mm Hg or unless SBP is >220mm Hg (level V evidence).[125] When treatment is indicated, the BP should be lowered cautiously and parenteral agents such as IV nicardipine or IV labetalol that are easily titrated are recommended.[124] In a preliminary study, patients with acute ischaemic stroke treated with IV nicardipine had an improved graded neurological exam score after 3 months (section 4.3.3).[86] However, given the small number of patients enrolled in this study (n = 43), it was not powered to determine whether the clinical outcome was statistically significant. Therefore, larger well controlled studies are needed to more fully assess the efficacy of this agent in this indication.

The goal of treatment for patients with pre-eclampsia is to lower elevated BP and thus prevent complications for the mother. Treatment does not alter the underlying pathophysiology, but it may slow its progression and allow time for the development of the fetus. Agents recommended for the treatment of pre-eclampsia in the US include hydralazine, labetalol, nifedipine and nitroprusside.[109] Preliminary data indicate that IV nicardipine effectively managed hypertension in pregnant women with pre-eclampsia (section 4.4).

To date, nitroprusside is the most commonly used agent in the short-term control of hypertension in children and adolescents, with IV labetalol also being increasingly used.[126] However, limited data also indicated that IV nicardipine may have a place in the rapid reduction of BP in this age group in the perioperative or intensive care settings (sections 4.2.5 and 4.6.1). Well designed trials are required to confirm the efficacy and tolerability (especially in regard to hypotension and tachycardia) of IV nicardipine in this patient population. Therefore, as is the case when treating severely hypertensive children with any hypertensive agent, these patients

should be cared for in the intensive care setting where BP and the effects of treatment can be closely monitored.[126]

Smaller open-label studies have also indicated potential benefits of IV nicardipine in a variety of other indications, including patients with acute aortic dissection, in patients receiving ECT, in patients with premature labour and in patients with Raynaud's phenomenon (sections 4.5 and 4.8–4.10). However, larger well designed trials will be needed to confirm the efficacy and tolerability of this agent in these various patient groups.

In summary, an IV formulation of nicardipine was as effective as a continuous infusion of IV nitroprusside in the short-term reduction of BP in well designed studies in patients with severe or postoperative hypertension. A potential role for IV nicardipine in the intraoperative acute control of BP in patients undergoing various surgical procedures (including cardiovascular, neurovascular and abdominal surgery), and in the deliberate induction of reduced BP in surgical procedures in which haemostasis may be difficult (e.g. surgery involving the hip or spine), has been demonstrated in preliminary studies. Preliminary studies also indicated the ability of a bolus dose of IV nicardipine to attenuate the hypertensive response, but not the increase in tachycardia, after laryngoscopy and tracheal intubation in anaesthetised patients. In large, well designed studies, IV nicardipine prevented cerebral vasospasm in patients with recent aneurysmal subarachnoid haemorrhage; however, overall clinical outcomes at 3 months were similar to those in patients who received standard management. Small preliminary studies have investigated the use of IV nicardipine in a variety of other settings, including acute intracerebral haemorrhage, acute ischaemic stroke, pre-eclampsia, acute aortic dissection, premature labour and ECT.

In conclusion, the efficacy of IV nicardipine in the short-term treatment of hypertension in settings for which oral therapy is not feasible or not desirable is well established. The ability to titrate IV nicardipine to the tolerance level of the individual patient makes this agent an attractive option, especially in critically ill patients or those undergoing surgery. Potential exists for further investigation of the use of this agent in clinical settings where a vasodilatory agent with minimal inotropic effects is appropriate.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opporutnity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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