Nicardipine HCL: clinical experience in patients undergoing anaesthesia for intracranial aneurysm clipping

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Previous studies have reported haemodynamic interactions between dihydropyridine calcium antagonists and general anaesthesia. During anaesthesia for intracranial aneurysm surgery, we prospectively compared haemodynamic values obtained from 13 patients being treated with nicardipine HCl (0.15 mg · kg^{-1} · hr^{-1} IV) for cerebral vasospasm against values obtained from 11 untreated controls. Prior to induction of anaesthesia, nicardipine-treated patients had significantly elevated mean ± SD cardiac index (5.67 ± 1.30 vs 3.99 ± 0.73 L · min^{-1} · m^{-2}) while MAP (86 ± 10 vs 99 ± 14 mmHg) and systemic vascular resistance (647 ± 227 vs 1141 ± 404 dynes · sec^{-1} · cm^{-5}) were reduced. Heart rate, CVP, and PACWP were similar between groups. Anaesthesia induction and tracheal intubation resulted in similar haemodynamic values between groups with the exception of CVP (10 ± 5 vs 5 ± 2 mmHg) and PACWP (15 ± 5 vs 8 ± 3 mmHg) which were elevated in the nicardipine group ($P < 0.01$). Mannitol infusion and deliberate hypotension resulted in nearly identical haemodynamic responses in both groups. Nicardipine-treated patients required more intravenous fluids during the operative procedure (2.4 ± 0.3 L vs 1.5 ± 0.4 L, $P < 0.05$) and were less likely to require isoflurane supplementation to morphine sulphate/nitrous oxide anaesthesia ($P < 0.01$). In summary, our experience with nicardipine HCl revealed no major untoward effects with respect to maintenance of intraoperative haemodynamic stability despite continuous antivasospasm therapy with this vasodilator.

Key words
ANAESTHESIA: neurosurgical; intracranial aneurysm; ANAESTHETIC TECHNIQUES: hypotension; BRAIN: blood flow, vasospasm; COMPLICATIONS: cardiovascular; MEASUREMENT TECHNIQUES: blood pressure, cardiac output; PHARMACOLOGY: calcium antagonists, nicardipine, drug interactions.

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Presented at the 9th World Congress of Anesthesiologists, May 26, 1988, Washington, D.C.

Among hospitalized patients with aneurysmal subarachnoid haemorrhage (SAH), the leading cause of morbidity and mortality is cerebral vasospasm.[1] Current experimental approaches toward pharmacologic treatment of vasospasm have focused on the use of agents which inhibit calcium entry into vascular smooth muscle.[2] One such agent, nicardipine HCl, a dihydropyridine derivative, has been proposed to have a potentially beneficial action because of its preferential cerebrovascular activity.[3] Although nicardipine-induced cerebrovascular relaxation has been documented in cats subjected to experimental vasospasm,[4] the safety and efficacy of nicardipine therapy in treating human vasospasm remains under investigation.[5]

Our institution was recently involved in a nicardipine dose-escalation study designed to determine maximally tolerated IV doses in patients with aneurysmal SAH.[5] Nicardipine is a potent peripheral vasodilator.[3,6] Because current therapy dictates continuous IV administration of this agent throughout the perioperative period,[5,7] untoward haemodynamic interactions between nicardipine and anaesthetic management of patients for aneurysm surgery are possible. The purpose of this study, therefore, was not so much to seek physiologic mechanisms by which nicardipine might interact with anaesthetic agents, but rather to determine if titration of doses of routine anaesthetic drugs and adjuvants used during craniotomy for aneurysm clipping would allow a stable haemodynamic state in the presence of this vasodilator.

Methods

This study was approved by our institutional human investigation committee and written consent was obtained from all participating patients. All patients were ASA

physical status II or III and had angiographically documented intracranial aneurysm(s) with SAH. The dose-escalation study involved successive groups of patients who received progressively higher doses of nicardipine HCl (Syntex, Palo Alto, CA) at a constant infusion rate.[5] Our study was initiated with the group receiving the maximal dose dictated by the protocol ($0.15\ mg \cdot kg^{-1} \cdot hr^{-1}$) which remained unchanged throughout the perioperative period. Thirteen patients receiving this dose of nicardipine were compared with eleven who received none (controls). Patients designated to receive nicardipine were so chosen by conforming to a strict protocol allowing participation in the dose-escalation study.[5] Infusion of nicardipine was commenced immediately after angiographic evidence for an intracranial aneurysm was obtained. The control patients were contemporaries who did not enter that study.

All patients were brought to the operating room unpremedicated where arterial (radial) and pulmonary artery (via basilac vein) catheters were placed. Awake (pre-induction) haemodynamic measurements included systolic, diastolic, and mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), mean pulmonary artery pressure (PAP), and mean pulmonary artery capillary wedge pressure (PACWP). Cardiac output, as determined by thermodilution in triplicate, allowed calculation of cardiac index (CI) and systemic vascular resistance (SVR). Blood samples were drawn for determination of arterial and mixed venous blood gases, as well as plasma nicardipine concentration (Syntex, Palo Alto, CA).

Anaesthesia was then induced with thiopentone ($4\ mg \cdot kg^{-1}$), morphine sulphate ($0.25\ mg \cdot kg^{-1}$), and pancuronium ($0.1\ mg \cdot kg^{-1}$) IV. When the airway was controlled with mask ventilation, hyperventilation was begun ($PaCO_2$ = 25–30 mmHg) and nitrous oxide (70 per cent) was added to the inspiratory gas mixture. Isoflurane (0.2–3.0 per cent delivered) was administered as required to maintain systolic blood pressure <120 mmHg. After complete neuromuscular blockade was achieved, the patients' tracheas were intubated and 10 min later the above haemodynamic and blood gas measurements were repeated. All patients then received mannitol ($0.5–1.0\ gram \cdot kg^{-1}$) IV over 20 min with the measurements repeated 10 min later. Induced hypotension, as indicated by surgical requirements, was achieved with IV sodium nitroprusside (SNP) infusion. Haemodynamic variables and blood gases were assessed with MAP = 60 and 50 mmHg respectively. After successful surgical clipping of the aneurysm, SNP was discontinued and 45 min later final measurements were obtained during closure of the galea. In the post-hypotensive interval and during emergence from anaesthesia, IV propranolol and hydralazine were administered as required to maintain heart rate < 90 bpm and systolic BP < 140 mmHg respectively. Total IV fluids administered during the anaesthetic as well as estimated surgical blood loss were recorded. Data were analyzed by Chi-square analysis, unpaired student's t-test, and 2-way analysis of variance (treatment group × anaesthetic interval) with post-hoc multiple comparison testing where indicated by a significant F ratio. Values are reported as mean ± SD with significance assumed when $P < 0.05$.

TABLE I Demographic data for nicardipine-treated and control patients

	Control	*Nicardipine*
Age (years)	52 ± 11	45 ± 12
Sex (M/F)	4/7	5/8
Days s/p SAH	9 ± 7	8 ± 6

Results

There were no statistically significant differences between groups with respect to age, sex, or the interval (days) between onset of SAH symptoms and surgery (Table I). Analysis of blood gases (arterial and mixed venous) was also without difference between groups at each interval throughout the study period. Prior to the induction of anaesthesia, MAP and SVR were lower ($P < 0.05$) while CI was higher ($P < 0.01$) in nicardipine-treated patients versus untreated controls (Table II). In contrast, heart rate, PACWP, PAP, and CVP values were similar between groups. At 10 min post-intubation, values for all variables were similar between groups with the exception of CVP, PAP, and PACWP which were greater ($P < 0.01$) in the nicardipine-treated patients. In the nicardipine group MAP was unchanged from pre-induction values (Figure). To the contrary, MAP was reduced in control patients when compared with pre-induction values ($P < 0.05$). Unintentional hypotension during the induction sequence (defined as systolic BP < 90 mmHg) occurred with similar frequency in nicardipine-treated patients (3 of 13) vs control patients (3 of 11). During the same interval, a systolic BP < 80 mmHg occurred in no patient in either group.

During the induction and intubation sequence, the frequency that isoflurane administration was required to manage systolic blood pressure was significantly less ($P < 0.01$) in nicardipine-treated patients (3 of 13 patients). In these three patients, the maximum isoflurane concentration derived was 0.5 per cent. In contrast, 9 of 11 control patients received isoflurane with doses administered varying from 0.5 to 3 per cent. Despite this, MAP was similar between groups (nicardipine = 78 ± 16 mmHg; control = 74 ± 15 mmHg). Ten min post-mannitol infusion, values were similar between groups for all variables measured. During SNP-induced hypoten-

TABLE II Haemodynamic values throughout anaesthesia for intracranial aneurysm surgery in patients with and without nicardipine therapy for vasospasm

	HR (*beats·min^{-1}*)	*MAP* (*mmHg*)	*PACWP* (*mmHg*)	*CVP* (*mmHg*)	*CI* (*L·min^{-1}·m^{-2}*)	*SVR* (*dynes·sec·cm^{-5}*)
Pre-Induction						
Nicardipine	82 ± 13	86 ± 10[a]	14 ± 6	8 ± 5	5.67 ± 1.30[b]	647 ± 227[b]
Control	78 ± 16	99 ± 14	12 ± 4	7 ± 3	3.99 ± 0.73	1141 ± 404
Post-intubation (10 min)						
Nicardipine	86 ± 21	78 ± 16	15 ± 5[b]	10 ± 5[b]	4.60 ± 2.10	747 ± 237
Control	83 ± 18	74 ± 15[c]	8 ± 3	5 ± 2	3.26 ± 1.32	954 ± 336
Post-mannitol (10 min)						
Nicardipine	74 ± 15	75 ± 7	14 ± 6	9 ± 5	4.48 ± 1.42	682 ± 200
Control	77 ± 15	71 ± 16	13 ± 6	8 ± 4	3.72 ± 0.98	815 ± 324
MAP = 60 mmHg						
Nicardipine	70 ± 15	60 ± 1	10 ± 4	6 ± 4	4.54 ± 1.29[a]	6.14 ± 271
Control	72 ± 14	61 ± 1	8 ± 5	4 ± 4	3.20 ± 0.92	829 ± 248
MAP = 50 mmHg						
Nicardipine	83 ± 10	50 ± 1	9 ± 4	6 ± 4	4.33 ± 1.30[a]	545 ± 294
Control	76 ± 14	50 ± 1	7 ± 5	5 ± 4	3.18 ± 0.93	669 ± 203
Craniotomy closure						
Nicardipine	75 ± 11	82 ± 8	13 ± 3	9 ± 5	3.47 ± 1.17	935 ± 4.47
Control	75 ± 11	84 ± 16	11 ± 4	8 ± 3	3.72 ± 1.53	1008 ± 363

Values = mean ± SD. a = $P < 0.05$; b = $P < 0.01$ comparing nicardipine (n = 13) vs control (n = 11) groups at respective perioperative intervals. c = $P < 0.05$ comparing pre-induction to post-intubation values within treatment groups.

sion (MAP = 60 and 50 mmHg), haemodynamic values remained comparable between groups with the exception of CI which was higher in the nicardipine group ($P < 0.05$). During craniotomy closure, no differences between groups could be detected in any of the variables measured. Pre-induction plasma nicardipine levels were 228 ± 56 ng·ml^{-1} in nicardipine-treated patients.

Total IV fluid volume administered was significantly greater ($P < 0.05$) in the nicardipine group (2.4 ± 0.3 L) vs controls (1.5 ± 0.4 L) despite a similar estimated surgical blood loss between groups (nicardipine = 372 ± 213 ml; control = 312 ± 114 ml). No patients required administration of sympathomimetic agents for blood pressure support. Total hydralazine and propranolol administered during craniotomy closure were not different between groups (nicardipine: 7.7 ± 12 mg, 1.2 ± 1.3 mg; control: 11.4 ± 16 mg, 1.4 ± 1.7 mg respectively).

Discussion

Strict control of arterial blood pressure is a necessary component of anaesthesia for intracranial aneurysm surgery. Although the haemodynamic effects of nicardipine HCl have been widely studied in conscious humans,[8] reports on the interaction between this drug and haemodynamic variables in the anaesthetized patient have been few.[9,10] Kishi *et al.* observed that bolus injection of nicardipine (0.5–1.5 mg) is safe and effective in reducing acute intraoperative hypertension.[9] However, the doses administered in their study were significantly less than those received by patients in our study. In the dog, Hysing *et al.* found that hypotensive properties of nicardipine and isoflurane were additive resulting mainly from isoflurane-induced inhibition of the reflex tachycardia elicited by nicardipine.[11] Using retrospective analysis, Stullken *et al.* found that nimodipine, another dihydropyridine calcium-antagonist, resulted in reduced arterial blood pressure throughout anaesthetics given for aneurysm surgery when compared with untreated patients.[12] In addition to these haemodynamic considerations, numerous other interactions between calcium antagonists and anaesthetic agents have been reported.[13,14] Because the frequency of administration of nicardipine HCl to treat cerebral vasospasm is expected to increase,[5] we felt that preliminary information on the safety of administering anaesthesia to patients with high-dose nicardipine infusion in progress should be obtained. Our results indicate that the presence of nicardipine had only minor significance in delivering a successful anaesthetic.

Prior to the induction of anaesthesia, nicardipine-treated SAH patients were found to have significantly lower MAP and SVR while CI was significantly higher than was observed in untreated controls. Similar

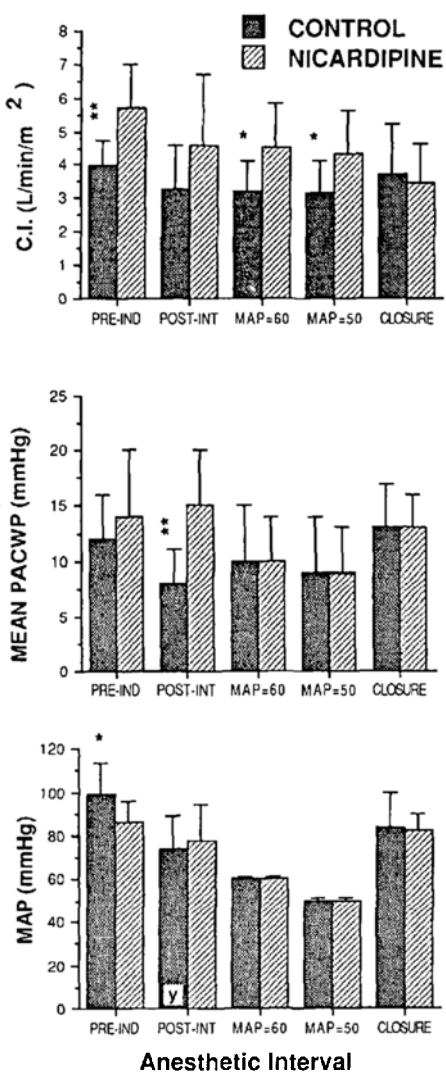

FIGURE Cardiac index (CI), mean pulmonary artery capillary wedge pressure (PACWP), and mean arterial pressure (MAP) at various stages of the anaesthetic (PRE-IND = awake; POST-INT = 10 min after intubation; MAP = 60 mmHg and 50 mmHg during induced hypotension; during galeal closure). Values = mean ± SD * = $P < 0.05$; ** = $P < 0.01$ comparing nicardipine vs control patients at each anaesthetic interval. y = $P < 0.05$ comparing pre-induction to post-intubation values within the control group.

nicardipine-induced haemodynamic changes have been reported in awake healthy human volunteers.[15] These changes in our patients were not accompanied by tachycardia and this differs from previous reports in awake patients.[8,16,17] Those studies, however, evaluated acute responses to the administration of nicardipine while in our patients the average duration of nicardipine administration was seven days before surgery. Resetting of the baroreflex with recovery from tachycardia during chronic administration of nicardipine has been reported previously.[18,19]

Induction of anaesthesia and tracheal intubation resulted in similar values for CI, SVR, and MAP between groups. Although MAP in the nicardipine group was statistically unchanged from awake values, MAP was decreased by 25 per cent ($P < 0.05$) over the same interval in control patients. At the same time CVP, PACWP, and PAP were significantly greater in nicardipine versus control patients. Although relatively large standard deviations in CI and SVR preclude elucidation of the underlying mechanisms for these differences, our clinical impression is that the stability of MAP and greater venous pressures in the nicardipine group were due to restriction of isoflurane administration as well as IV fluid therapy administered during the induction sequence. The latter point is supported by the observation that nicardipine patients received significantly more fluids during the course of the anaesthetic.

Induced hypotension was well tolerated by patients in both groups. Unfortunately, we did not quantitate the SNP dose required to achieve MAP = 50 and 60 mmHg for comparison between groups. However, both groups demonstrated a rapid recovery from hypotension upon discontinuation of nitroprusside and dosage requirements for hydralazine and propranolol to treat rebound hypertension were similar between groups.

In summary, our experience with nicardipine HCl during anaesthesia for intracranial aneurysm surgery revealed no major untoward effects in maintenance of haemodynamic stability despite the presence of high doses of this vasodilator. Conclusions from our investigation are limited to the specific anaesthetic regimen described, but the data suggest that haemodynamic control can be readily achieved during anaesthesia for intracranial aneurysm surgery despite continuous anti-vasospasm therapy with nicardipine HCl.

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Résumé

Des études antérieures ont rapporté des intéractions hémodynamiques entre les antagonistes du calcium dihydropyridine et l'anesthésie générale. Durant l'anesthésie pour résection d'un anéurysme intracrânien, on a comparé d'une façon prospective les valeurs hémodynamiques obtenues chez treize patients ayant été traités avec la nicardipine HCl ($0.15\ mg \cdot kg^{-1}hre^{-1}$ IV) pour vasospasme cérébral avec des valeurs obtenues chez onze patients contrôle non traités. Avant l'induction, les patients traités à la nicardipine avaient une élévation significative de la valeur moyenne ± SD de l'index cardiaque (5.67 ± 1.30 vs $3.99 \pm 0.73\ L \cdot min \cdot^{-1} m^{-2}$) alors que la pression artérielle moyenne (86 ± 10 vs 99 ± 14 mmHg) et la résistance vasculaire systémique (647 ± 227 vs 1141 ± 404 dynes $\cdot sec^{-1} \cdot cm^{-5}$) étaient diminuées. La fréquence cardiaque, la pression veineuse centrale et la pression bloquée de l'artère pulmonaire étaient similaires dans les deux groupes. L'induction de l'anesthésie et l'intubation ont produit des valeurs hémodynamiques similaires entre les groupes à l'exception de la pression veineuse centrale (10 ± 5 vs 4 ± 2 mmHg) et la pression bloquée de l'artère pulmonaire (15 ± 5 vs 8 ± 3 mmHg) qui étaient élevées dans le groupe nicardipine ($P < 0.01$). La perfusion de mannitol et l'hypotension contrôlée ont amené des réponses hémodynamiques quasi identiques dans les deux groupes. Les patients traités à la nicardipine ont requis plus de liquide lors de la procédure chirurgicale (2.4 ± 0.3 L vs 1.5 ± 0.4 L, $P < 0.05$) et avaient tendance à recevoir moins d'isoflurane supplémentaire lors d'une anesthésie au sulfate de morphine/protoxyde d'azote ($P < 0.01$). En résumé, notre expérience avec HCl nicardipine n'a pas démontré d'effets secondaires sur la stabilité hémodynamique peropératoire malgré la continuation de la thérapie antispasmodique avec ce vasodilatateur.