Captopril Reduces the Dose Requirement for Sodium Nitroprusside Induced Hypotension

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The authors studied 12 patients who required deliberate hypotension for spinal fusion operations in order to investigate the efficacy of captopril for reducing dose requirement for sodium nitroprusside (SNP). Six patients, selected at random, were pretreated with captopril, 3 mg/kg po, and the remaining six patients served as controls. All patients received a similar anesthetic technique, consisting of thiopental 3 mg/kg, pancuronium 0.1 mg/kg, morphine 0.5 mg/kg, plus nitrous oxide 70% in oxygen. SNP was used to maintain mean arterial pressure (MAP) at 50–55 mmHg during deliberate hypotension lasting 140 ± 13 minutes (mean $\pm$ SE). Patients who received captopril required less SNP than untreated patients both early during hypotension (1.4 ± 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. 4.8 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, $P < 0.05$), as well as late during hypotension (2.2 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ vs. 5.6 ± 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, $P < 0.05$). Whole blood cyanide was significantly lower in the patients pretreated with captopril than the untreated controls both early in the hypotensive period (2.7 ± 0.6 $\mu mol/l$ vs. 13 ± 4 $\mu mol/l$, $P < 0.05$) and also late in the hypotensive period (3.7 ± 0.8 $\mu mol/l$ vs. 30 ± 10 $\mu mol/l$, $P < 0.05$). MAP was reduced by captopril pretreatment both following induction of anesthesia (64 ± 4 mmHg captopril vs. 80 ± 4 mmHg control, $P < 0.05$) and during surgery before deliberate hypotension (86 ± 5 mmHg captopril vs. 100 ± 4 control, $P < 0.05$). Cardiac output did not differ significantly between the groups, either awake or after anesthetic induction. The authors conclude that captopril pretreatment significantly reduces the dose of SNP required to produce deliberate hypotension and, therefore, reduces the potential for cyanide toxicity. No adverse hemodynamic consequences of combining captopril with thiopental, N_2O, or morphine anesthesia were observed. (Key words: Anesthetic techniques: hypotension, nitroprusside. Polypeptides: renin-angiotensin. Pharmacology: captopril; nitroprusside. Sympathetic nervous system: catecholamines. Toxicity: cyanide.)

DELIBERATE HYPOTENSION is an accepted intraoperative technique for reducing blood loss, improving surgical

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conditions, and decreasing the risk of vascular aneurysm rupture. Infusions of SNP commonly are used to reduce arterial pressure because of the rapid onset and termination of effect of this drug. Despite its attractive pharmacodynamics, SNP infusion is associated with increased blood cyanide levels, and deaths due to apparent cyanide poisoning have been reported.[1] Limiting infusion rate and total dose minimizes the risk of cyanide intoxication,[2-4] but this approach also may limit the usefulness of the drug, especially in patients in whom the dose requirement for SNP is great. In operations where prolonged SNP infusion is anticipated, a technique that would minimize the dose requirement for SNP would be of particular value.

Plasma renin activity increases during SNP hypotension, and the renin angiotensin system is thought to be at least partially responsible for resistance to SNP.[5] Renin cleaves the peptide angiotensinogen to form angiotensin I, which in turn is cleaved by converting enzyme, producing the potent vasoconstrictor angiotensin II. Angiotensin II appears to be an important physiologic mechanism opposing SNP-induced vasodilation. Recently the converting enzyme inhibitor, captopril, became available for the treatment of hypertension.[6] By inhibiting the generation of angiotensin II, captopril blocks the cardiovascular effects of the renin–angiotensin system. Jennings et al.[7] have demonstrated an enhanced hypotensive response to SNP in awake human volunteers following treatment with captopril. The present study investigates the effectiveness of captopril for potentiating the hypotension produced by SNP, as well as the impact of captopril on the cardiovascular system during general anesthesia and surgery.

Methods

Twelve patients with adolescent idiopathic scoliosis (ages 12–36 years) who required deliberate hypotension during elective posterior spinal fusion surgery were studied. The protocol was approved by the local human studies committee, and informed consent was obtained from each patient or his appropriate relative. Premedication consisted of diazepam, 5–10 mg po, 1 h before surgery. Six patients were selected to receive captopril by random lot; the remainder served as controls. Captopril, 3 mg/kg, was administered po with a sip of water just prior to transport to the operating suite. Anesthesia was induced

TABLE 1. Hemodynamic and Catecholamine Data

		Awake	Anes	Surg	Early SNP	Late SNP	Post SNP
MAP	Captopril	70 ± 5	64 ± 4*	86 ± 5*†	57 ± 2	54 ± 1	82 ± 5†
(mmHg)	Control	95 ± 5	80 ± 4	100 ± 4†	59 ± 4†	57 ± 3†	87 ± 5
Cardiac output	Captopril	6.0 ± 0.7	5.1 ± 0.3	6.1 ± 0.6	5.8 ± 0.8	5.8 ± 0.8*	5.8 ± 0.7
(1/min)	Control	7.1 ± 1.1	4.8 ± 0.5	6.8 ± 0.7†	6.6 ± 0.4†	7.7 ± 0.5†	5.2 ± 0.2
SVR	Captopril	998 ± 92	974 ± 103	1,134 ± 130	796 ± 123	777 ± 72*	1,028 ± 81
(dyn·sec·cm^{-5})	Control	1,046 ± 87	1,266 ± 114	1,158 ± 142	707 ± 78†	592 ± 60†	1,214 ± 67
Heart rate	Captopril	78 ± 3	102 ± 7	90 ± 7	92 ± 8	93 ± 8	83 ± 8
(beats·min^{-1})	Control	93 ± 9	93 ± 3	89 ± 6	106 ± 3	103 ± 8	76 ± 6
Epinephrine	Captopril	39 ± 27	31 ± 17	188 ± 82	508 ± 185†	716 ± 277	249 ± 68†
(pg/ml)	Control	77 ± 29	16 ± 3	109 ± 42	481 ± 256	338 ± 112*	200 ± 72
Norepinephrine	Captopril	285 ± 135	310 ± 146	337 ± 130	754 ± 277†	697 ± 159	642 ± 237
(pg/ml)	Control	345 ± 135	206 ± 100	334 ± 141	568 ± 230	645 ± 334†	456 ± 273

Values are mean ± SEM.   † $P < 0.05$, *versus* Anes. value.
* $P < 0.05$, *versus* control group.

with thiopental, 3 mg/kg, and pancuronium, 0.1 mg/kg, was administered to facilitate endotracheal intubation. Anesthesia was maintained with morphine, 0.5 mg/kg,

FIG. 1. Whole blood cyanide before, during, and after sodium nitroprusside (SNP) infusion. All values = mean ± SEM. * = $P < 0.05$ captopril *versus* control.

and nitrous oxide, 70% in oxygen. Surgery was performed with patients in the prone position on the Relton Hall frame in order to reduce pressure on the abdomen. Hemodynamic monitoring consisted of a radial artery cannula and a thermistor-tipped, flow-directed, catheter placed in the pulmonary artery using pressure waveform guidance. Arterial blood was obtained for analysis of converting enzyme activity, plasma renin activity, whole blood cyanide, and plasma catecholamines.

Chemical assays and cardiovascular variables were measured at the following times: 1) awake; 2) following induction of anesthesia and endotracheal intubation; 3) following skin incision; 4) immediately after a stable level of hypotension (MAP 50–55 mmHg) had been established with SNP: "early hypotension"; 5) immediately before the end of hypotension: "late hypotension" (mean duration of hypotension 140 min ± 39 SD); and 6) when arterial pressure had stabilized after discontinuing SNP. SNP dose was decreased in increments in an effort to avoid rebound hypertension.

Converting enzyme activity was assayed using the procedure and materials supplied by Ventrex Laboratories (Portland, Maine). Samples were assayed in duplicate and the results averaged. Converting enzyme was allowed to cleave a tritiated tripeptide (^{3}H-hippuryl-glycyl-glycine) and the liberated ^{3}H-hippuric acid was extracted and counted as a measure of enzyme activity. Plasma renin activity was determined by radioimmunoassay using materials and procedures supplied by New England Nuclear (N. Billerica, Massachusetts). Samples for plasma renin activity were assayed in duplicate and the results averaged. Whole blood cyanide was measured using the method of Rodkey *et al.*[8,9] Cyanide was liberated as HCN gas from acidified whole blood, and the gas was passed through a solution of sodium hydroxide in order to trap the cyanide in the alkaline solution. Following extraction, the cyanide
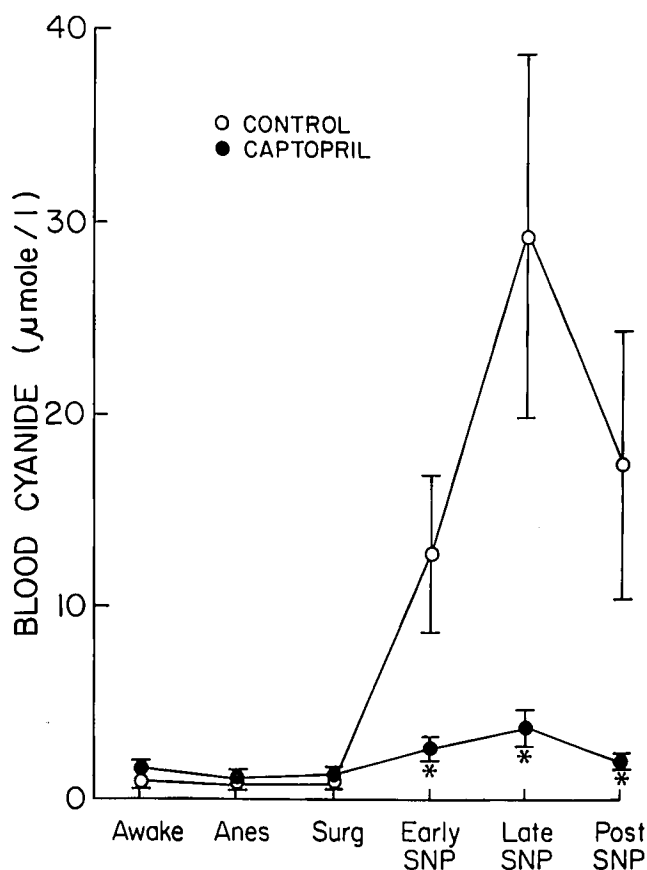
was reacted with pyridine–pyrazolone dye and quantitated by the spectral absorbance of the dye at 620 nm. The system was calibrated by assaying standard KCN solutions of known concentrations as determined by $AgNO_3$ titration.[10] Blood cyanide samples were protected from light during storage and assay procedure to prevent in vitro degradation of SNP,[11] however, work by Arnold et al. suggests that this precaution may not be necessary.[12] High-pressure liquid chromatography with electrochemical detection (Bioanalytical Systems, Lafayette, Indiana) was used for assay of plasma catecholamines.[13] The lowest limit of detection is 30 pg/ml for norepinephrine and epinephrine.

Data obtained during anesthesia were compared by analysis of covariance and Duncan's multiple range test, using awake values as a covariant.[14] $P < 0.05$ was regarded as significant.

Results

Mean arterial pressure was significantly less after captopril treatment (table 1), both following induction of anesthesia and during surgical stimulation. There was, however, no significant difference in mean arterial pressure between the two groups during or after the SNP infusion.

Pretreatment with captopril significantly reduced the dose of SNP required to produce similar degrees of hypotension both early in the course of hypotension (1.4 ± 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [mean $\pm$ SE], captopril vs. 4.8 ± 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ control) and late in the course of hypotension (2.2 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ captopril vs. 5.6 ± 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ control).

Cardiac output values were similar for the two groups throughout the course of SNP infusion, although only the control group developed a significant increase in cardiac output during surgery and controlled hypotension.

The systemic vascular resistances differed significantly between the captopril and control groups only late in the course of SNP infusion. However, a significant reduction in SVR only occurred during hypotension in the control group. Heart rate was similar in the two groups throughout.

Whole blood cyanide (fig. 1) was similar in the two groups (1.6 ± 0.4 $\mu mole/l$ captopril vs. 0.9 ± 0.3 $\mu mol/l$ control) prior to nitroprusside infusion. Blood cyanide values increased significantly during SNP infusion in control patients and were significantly greater than in captopril patients, both early (2.7 ± 0.6 $\mu mol/l$ captopril vs. 13 ± 4 $\mu mol/l$ control) and late (3.7 ± 0.8 $\mu mol/l$ captopril vs. 30 ± 10 $\mu mol/l$ control) in the course of hypotension as well as after SNP was stopped.

Converting enzyme activity (fig. 2) was reduced throughout in those receiving captopril. The awake values for converting enzyme activity were 47 ± 11 $nmol \cdot ml^{-1} \cdot min^{-1}$ captopril versus 104 ± 13 nmol
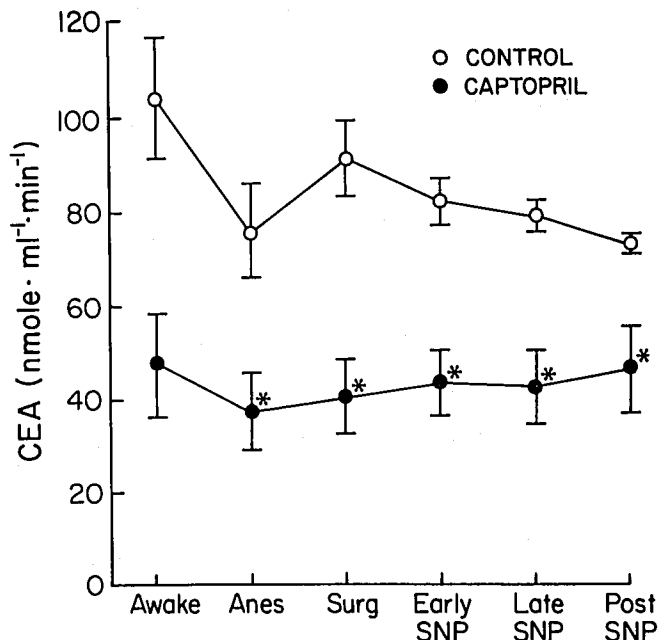
FIG. 2. Converting enzyme activity (CEA) before, during, and after SNP infusion. All values = mean $\pm$ SEM. * = $P < 0.05$ captopril versus control.

$\cdot ml^{-1} \cdot min^{-1}$ control and following SNP infusion were 46 ± 9 $nmol \cdot ml^{-1} \cdot min^{-1}$ captopril versus 73 ± 2 $nmol \cdot ml^{-1} \cdot min^{-1}$ control.

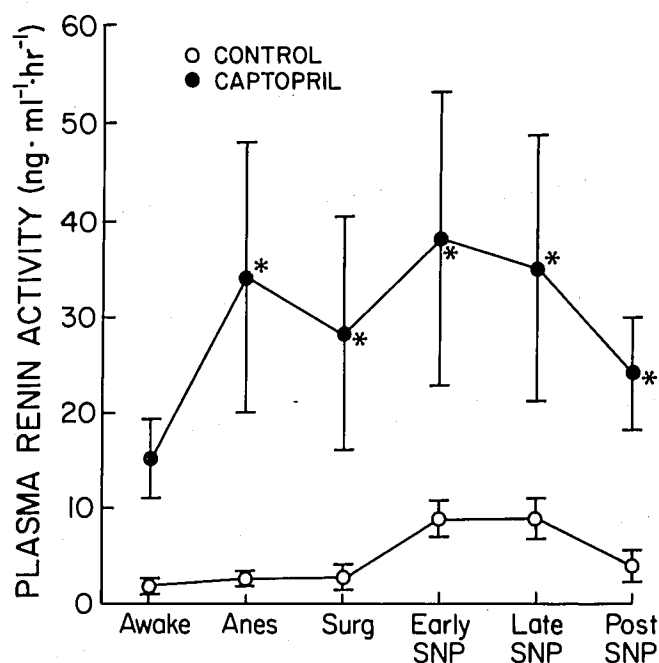Plasma renin activity (fig. 3) was greater throughout the operative period in those receiving captopril (15

FIG. 3. Plasma renin activity before, during, and after SNP infusion. All values = mean $\pm$ SEM. * = $P < 0.05$ captopril versus control.

$ng \cdot ml^{-1} \cdot h^{-1} \pm 4$ SE) as compared with the untreated patients (1.8 $ng \cdot ml^{-1} \cdot h^{-1} \pm 0.9$ SE). This difference persisted until the end of the protocol when, following SNP infusion, plasma renin activity values were 24 $ng \cdot ml^{-1} \cdot h^{-1} \pm 6$ SE in those receiving captopril *versus* 3.8 ± 1.3 $ng \cdot ml^{-1} \cdot h^{-1}$ in the untreated patients.

Plasma epinephrine and norepinephrine tended to increase during controlled hypotension but values were essentially similar for the two groups at all times (table 1).

Discussion

The present study demonstrates that the potentiation of SNP-induced hypotension by captopril is clinically useful in reducing the dose of SNP required to produce intraoperative controlled hypotension. Concomitant with the reduction in SNP dose requirement is a marked decrease in blood cyanide levels. Previous investigators observed increases in plasma renin activity accompanying the infusion of SNP and concluded that activation of the renin–angiotensin system is one physiologic mechanism opposing the hypotensive action of SNP.[5] In a study by Jennings of healthy volunteers, blockade of the renin–angiotensin cascade by captopril potentiated the hypotensive action of SNP.[7] Indeed, whereas plasma renin activity increased significantly in untreated patients when SNP was infused, no such increase was observed in the patients receiving captopril. The increased plasma renin activity observed preoperatively in the patients receiving captopril was the result of the loss of feedback inhibition by angiotensin II on renin secretion[6,7] and is evidence of efficacy of the drug. Captopril inhibits converting enzyme and reduces generation of angiotensin II in spite of elevated levels of renin. Since it is angiotensin II, and not the enzyme renin, that is responsible for the vasopressor action associated with renin–angiotensin system activation, the increases in plasma renin activity in the presence of captopril have no hemodynamic consequence, *per se.*

The single oral dose of captopril produced an inhibition of converting enzyme activity that did not diminish during the surgical procedure. Following oral administration in awake volunteers, Kripalani *et al.* found that blood captopril level peaked in 30–90 min and its half-life was estimated to be less than 2 h.[15] In view of this short half-life, a relatively large dose of captopril was selected to ensure converting enzyme inhibition throughout the SNP infusion. Although this dose of captopril resulted in a significant reduction in arterial pressure in treated patients as compared with those untreated, no patient exhibited symptoms of hypotension while awake, nor did clinically serious decreases in arterial pressure occur with induction of general anesthesia. Cardiac output was not altered significantly by captopril administration before or after

induction of general anesthesia, further supporting the clinical impression that perfusion was well maintained. These observations, however, were made in patients without evidence of cardiovascular disease, so that the results should be applied with caution in patients with impaired cardiovascular reserve and in those receiving other antihypertensive therapy. Although not currently available, an intravenous preparation of captopril would allow the inhibition of converting enzyme activity to be delayed until just prior to SNP infusion.

The SNP infusion was discontinued gradually in an effort to avoid rebound hypertension, so that data concerning captopril's potential for diminishing rebound hypertension were not obtained. However, since the renin–angiotensin system appears to be responsible for rebound hypertension following SNP infusion,[16] captopril may decrease the severity of rebound hypertension by blocking the cardiovascular effects of renin secretion.

The increase in cardiac output observed late in the course of SNP infusion in untreated patients did not occur in those treated with captopril. Possibly, the increase in cardiac output is a response to histotoxic hypoxia produced by cyanide accumulation late in the course of the infusion; however, other indices of cyanide toxicity (increased mixed venous oxygen tension, metabolic acidosis) were not observed. Others have observed altered cardiovascular responses to hypotension following captopril administration, suggesting that baroreceptor responsiveness may be altered by captopril.[17]

In summary, we have shown that captopril significantly can reduce the dose of SNP required to produce deliberate hypotension during anesthesia and operation, as well as reduce the resulting concentration of blood cyanide. The mechanism for this effect appears to be directly through its actions on the renin–angiotensin system and not a secondary effect on the sympathetic nervous system, since plasma catecholamine responses to controlled hypotension were unaltered by captopril. In addition, no untoward reactions occurred when thiopental, nitrous oxide, and morphine anesthesia, and muscle relaxation with pancuronium were induced in patients pretreated with captopril.

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