Anesthesiology
77:646–655, 1992

Elderly, Conscious Patients Have an Accentuated Hypotensive Response to Nitroglycerin

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There is no adequate explanation for the highly variable response of systemic blood pressure to nitroglycerin (glyceryl trinitrate [GTN]). Aging produces cardiovascular changes that should alter the effects of GTN, but elderly patients usually have been excluded from studies of GTN. Accordingly, the authors compared the effects of GTN on systemic blood pressure in elderly and younger patients. Fifty-three patients, aged 49–87 (with 30 patients older than 70), were studied. Before elective vascular surgery, 14 patients received an infusion of placebo; 26, a constant infusion of GTN; and 13, a stepwise increasing infusion of GTN. After a standardized anesthetic induction and the start of surgery, the identical infusion protocols were repeated in each group. Data on GTN infusion rate, arterial blood pressure, and GTN concentrations *versus* time, age, and other potentially influencing variables were pooled for analysis. Before anesthesia and surgery, GTN more commonly caused excessive hypotension in patients older than 70 yr than in younger patients, but none of the patients had complications. A repeated-measures model analysis indicated that age significantly influenced the effects of GTN on blood pressure. That is, patients who are in their 70s who receive 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of GTN are predicted to experience a twofold greater decrease in systolic arterial pressure (approximately 33 mmHg) than patients in their 50s. However, no apparent effect of age on intraoperative GTN responsiveness was discernible nor was a predictable relationship found between the preoperative and intraoperative responsiveness or between arterial concentrations of GTN and blood pressure or age. Therefore, the authors conclude that, in the absence of the effects of anesthesia and surgery, elderly patients have a more pronounced blood pressure response to GTN than younger patients. Furthermore, the authors conclude that preoperative blood pressure responsiveness to GTN is not a reliable predictor of intraoperative responsiveness. (Key words: Age factors. Anesthetics, volatile: isoflurane. Blood pressure. Pharmacology: glyceryl trinitrate.)

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Received from the Departments of Anesthesia, Laboratory Medicine, and Surgery (Division of Vascular Surgery), School of Medicine; and the Department of Pharmacy, School of Pharmacy, University of California, San Francisco, California. Accepted for publication June 1, 1992. Supported by National Institutes of Health grant 2P01AG03104 and the Anesthesia Research Foundation, San Francisco, California.

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SURGICAL PATIENTS may require intravenous nitroglycerin (glyceryl trinitrate [GTN]) perioperatively to control blood pressure or relieve myocardial ischemia. However, seemingly comparable patients often need significantly different doses of GTN to effect the same hemodynamic results.[1,2] Acute tolerance[3] and differences in resting cardiac output[4] are known to affect the pharmacology of GTN, but these alone are insufficient to explain such differences. Age-related changes in pharmacokinetics or dynamics also may contribute. Although aortic tissue from senescent animals retains normal responsiveness to organic nitrates *in vitro*,[5] left ventricular compliance decreases with aging.[6] Accordingly, GTN-induced decreases in systemic venous return should reduce ventricular filling more in elderly than in younger patients.

Because age is an independent predictor of coronary atherosclerosis,[7] elderly patients frequently have myocardial ischemia, which is treated with GTN. However, previous studies of GTN usually have excluded elderly patients or have not explored the influence of age or anesthesia and surgery on the effects of GTN. A better understanding of the variables that alter the pharmacokinetics and dynamics of GTN should facilitate its safe administration, especially in elderly patients, who are least able to tolerate the prolonged myocardial ischemia that may result from inadequate dosing or the hypotension due to excessive dosing. Therefore, we designed the current study to answer three questions: 1) Are elderly patients more sensitive to the hypotensive effects of intravenous GTN than younger patients? 2) Are arterial concentrations of GTN and its major metabolites different in elderly patients than in younger patients? 3) Is the preoperative blood pressure response to intravenous GTN predictive of its intraoperative response? We selected systolic blood pressure as our primary variable for study because anesthesiologists commonly use it to define the acceptable GTN dose response.

Materials and Methods

PATIENT POPULATION AND PREPARATION FOR STUDY

With approval from our Committee on Human Research and written informed consent, we studied 53 pa-

tients (aged 49–87, including 30 patients older than 70 yr of age) scheduled for elective abdominal or femoral vascular surgery. We selected this population because they frequently have coronary atherosclerosis, often receive intravenous GTN for control of blood pressure or treatment of myocardial ischemia, and require invasive blood pressure monitoring. We excluded from study patients with uncontrolled congestive heart failure, valvular heart disease, jaundice, or end-stage renal disease.

On the night before study, all patients were given an intravenous infusion of 5% dextrose and one-half normal saline solution at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ through a catheter in the hand or wrist; administration of long-acting nitrates was stopped at least 8 h before surgery (except in two patients in whom a dose inadvertently was administered 100 min before study). At 5:00 AM the next morning, patients were given diazepam, 0.10–0.15 mg/kg orally, and their usual morning medications (except nitrates). Thirty minutes later, they received an intramuscular injection of morphine sulfate, 0.10–0.15 mg/kg, and were transported to a quiet operating room. The preoperative phase of the studies was conducted before the surgical nurses or surgeons arrived. Diazepam and morphine were administered to the patients to reduce their anxiety and discomfort during the preoperative preparations and to emulate common clinical practice in other patients given intravenous GTN (e.g., those having acute myocardial infarctions).

On arrival in the operating room, patients were placed in the supine position on a padded operating room table, intravenous fluid administration was increased to 5 $ml \cdot kg^{-1} \cdot h^{-1}$, and 2 l/min oxygen was administered through nasal prongs. With the patients under local anesthesia, we placed a 20-G catheter in a radial artery for measurement of blood pressure with 180-cm-long pressure tubing and a Trandec® disposable transducer (Pressure Monitoring Kit 51-MK9242, American Edward Laboratories, Irvine, CA). After the zero reference pressure was established and the transducer was calibrated, blood pressure and heart rate (from electrocardiographic monitoring) were recorded continuously (Gould model 2107-4490 00, Cleveland, OH). When all preparations for study were completed, patients rested quietly until their systolic arterial pressure (SAP) varied less than 10% for 2 min, which usually required 5–10 min. The transducer was checked frequently for zero drift during study and changes in calibration at the end of study. Drift detected during study (typically less than 2 mmHg) was corrected immediately, and calibration did not change.

Preoperative Study Protocol

In a single-blind design, the first 14 patients received an infusion of placebo for 30 min so that the stability of SAP during the experiment could be determined. The next 26 patients received a constant infusion of GTN for 15–30 min or until hypotension occurred, as defined by an SAP that was 85% of the SAP_W, the mean of the three lowest SAP values recorded by the ward nursing staff before study. We used the SAP_W value and not the SAP value immediately preceding the start of the study (SAP_0 is the average SAP for the 2 min preceding the start of GTN infusion) to define hypotension because the SAP_W usually was considerably less than the SAP_0 and thus better defined the minimum safe blood pressure. We adopted 15 min as the duration of GTN infusion after the first ten studies demonstrated stability of SAP within 10 min of the start of infusion. GTN (Tridil® [DuPont Pharmaceuticals, Inc., Wilmington, DE] diluted to 100 μg/ml in 5% dextrose) was administered from a 50-ml glass syringe with a calibrated syringe pump (model 1001, Medfusion Systems, Inc., Norcross, GA) into the indwelling intravenous catheter through low-absorption tubing (AVI Guardian Intravenous Administration Set, 3M Company, St. Paul, MN).

Our initial study design called for a GTN infusion rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, to be increased by 0.25 μg in subsequent patients if SAP declined to less than 10% of the SAP_0. However, the second patient to receive 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ showed significant hypotension that necessitated treatment with ephedrine. Subsequent patients received 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In 1 patient, an infusion pump malfunction resulted in an infusion rate of 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Thus, 14 patients received an infusion of placebo and 26 patients a constant infusion of GTN (23 patients received 0.5, 2 patients 0.75, and 1 patient 0.35 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

In 6 patients 70 years of age or older, the constant infusion of GTN was stopped before 15 min because hypotension developed. To confirm the apparent importance of age in this response, we studied 13 additional patients (9 were older than 70 yr) using a stepwise increasing infusion of GTN. This revised protocol tested the effects of three target doses of GTN: 0.25, 0.50, and 0.75 or 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ GTN. The 1.0-μg dose, and not the 0.75-μg dose, was given if 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ did not reduce the SAP to less than SAP_0. Each target dose was administered for 8 min and was preceded immediately by a 2-min loading dose to speed attainment of steady state and to confine the duration of the experiment to 30 min (the period of time our placebo studies documented stable hemodynamics). The loading dose (LD) was calculated as follows: $LD = 2 \cdot (TD - PD) + PD$, where TD is the target dose and PD is the preceding dose. For example, most patients were expected to receive a loading/target dose of 0.5/0.25, 0.75/0.5, and 1.0/0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion was stopped immediately if SAP decreased to less than 85% of SAP_W.

Intraoperative Study Protocol

Anesthesia and muscle relaxation were induced with 2–3 mg/kg thiopental, 1–3 μg/kg fentanyl, 0.5–1.5% inspired isoflurane, and 0.1 mg/kg vecuronium. After tracheal intubation, ventilation was controlled and anesthesia provided with 50% nitrous oxide and sufficient isoflurane to maintain the SAP at a level that was greater than or equal to the SAP_W. During induction of anesthesia and before incision, intravenous lactated Ringer's solution was administered by the responsible anesthesiologist (not an investigator) in a volume deemed necessary to maintain clinically acceptable hemodynamics. Pulmonary artery and central venous pressure monitoring were instituted before induction of anesthesia when clinically indicated. In the research protocol, it was required only that filling pressures be maintained in a normal range, if possible, when they were monitored (central venous pressure, 3–8 mmHg; pulmonary capillary wedge pressure, 5–12 mmHg) or in a range comparable (within 5 mmHg) to the baseline values (if available) obtained before the preoperative infusion.

During the first 30–60 min of surgery, when surgical stimulation was deemed to be stable (no extension of the incision, repositioning of retractors, or cessation of surgery) and before significant blood loss occurred or clamping of major vessels, the test infusion of placebo or GTN was administered again with exactly the same doses and timing used preoperatively. The infusion was stopped immediately if the SAP decreased to less than 85% of the SAP_W. End-tidal isoflurane concentrations and rate of fluid administration (5 $ml \cdot kg^{-1} \cdot h^{-1}$ of lactated Ringer's solution) were kept stable for at least 5 min before and during the GTN infusion. No additional medications were added during the infusion. All hemodynamic data and all drugs and fluids administered were recorded by the investigators. Between-group differences in demographics and hemodynamics were assessed by chi-square analysis and paired and unpaired *t* tests, as appropriate.

Arterial Concentrations of GTN and Metabolites

In patients receiving a constant infusion of GTN, we drew arterial blood samples immediately before infusion of GTN and at 2.5, 5, 10, 15, 20, 25, and 30 min after the start of the infusion. In patients receiving a stepwise increasing infusion of GTN, we drew arterial samples immediately before infusion and at 7.5 and 10 min after the start of each of the three planned steps in the infusion. All samples were drawn from the radial arterial catheter in an identical fashion by the same investigator. The blood samples were centrifuged immediately for 30 s at 14,000 rpm. The plasma was removed and frozen in a dry-ice bath of isopropyl alcohol until completion of the study, when the samples were transferred to a freezer for storage at −80° C until they were extracted and analyzed. The total time elapsed from the time the blood was drawn until the plasma was frozen was less than 2.5 min. Plasma concentrations of GTN and its two major metabolites (1,2 glyceryl dinitrate and 1,3 glyceryl dinitrate) were determined with the analysis published by Lee *et al.*[8] A brief summary of this technique and our pharmacokinetic analysis of the resulting data is presented in Appendix 1.

Data Analysis

Data were analyzed from the preoperative study for placebo or GTN infusion rates, SAP *versus* time, and influencing variables (age, gender, weight, previous nitrate exposure, and intravascular volume) for all patients. Nitrate exposure was considered positive if the patient received any form of nitrate therapy during the 24 h preceding study. Intravascular volume was defined as "potentially inadequate" (despite our design to standardize hydration) when a patient received 1 standard deviation less intravenous fluid than other patients over the 12 h preceding this study, in addition to bowel cathartics and intravenous dye injection for aortography during the 24 h preceding the study. Data were analyzed with the computer program NONMEM, which uses normal theory maximum likelihood estimation for an approximate model, linearized in its random effects, to estimate population pharmacokinetic and dynamic parameters describing mean effects of covariates (such as age) and interindividual and intraindividual variability.[9] The log likelihood ratio was used to test for significant improvement in model fit produced by including the various covariates (see table 3).[10] The same analysis technique was used for the intraoperative data except that the covariance (if any) between preoperative and intraoperative parameters also was evaluated. Details of this mathematical analysis are provided in Appendix 2.

Results

Patients receiving placebo and GTN were clinically and demographically comparable (table 1). Similarly, the younger group (younger than 70 yr) was comparable to the older group of patients, except this group included more women (table 2).

Preoperative Studies

Infusion of placebo had no significant effect on SAP or heart rate, whereas GTN decreased SAP (fig. 1) and increased heart rate 5%. In 10 of 23 patients older than 70 yr (5 patients given 0.5 and 1 given 0.75

TABLE 1. Demographic and Clinical Characteristics of Patients Given Placebo *versus* Glyceryl Trinitrate

	Placebo (n = 14)	GTN (n = 39)	*P* Value
Age (yr)*	66	69	NS
≥70 yr (%)	50	59	NS
Males (%)	43	64	NS
Weight (kg)*	67	72	NS
β blockers (%)	21	31	NS
Ca blockers (%)	14	26	NS
Nitrates (%)	29	10	0.10
Hx HTCVD (%)	71	72	NS
Hx angina (%)	21	13	NS
Hx MI (%)	14	13	NS

NS = not significant; Hx = history of; HTCVD = hypertension; MI = myocardial infarction.
* Mean values.

$\mu g \cdot kg^{-1} \cdot min^{-1}$, and 4 patients receiving the stepwise increasing infusion) and 3 of 16 younger patients (all given the stepwise increasing infusion), the study was stopped after 2–25 min because hypotension developed (SAP < 85% of SAP_W), but no patient had complications. In one patient, the study was stopped after 6 min because of urinary distress; in another patient, it was stopped after 5 min because of nausea. All data were used in the analysis until termination of the study.

The best fitting model (see Appendix 2 for definition of the models and parameters) indicated significant effects of age on the mean proportionality constant (m) linking the infusion rate of GTN and SAP and the mean monoexponential rate constant (k) (table 3). Weight also was found to significantly affect mean k (table 3). Addition of gender, prior nitrate exposure, or volume status did not further improve the model fit. The parameters in the final model for all patients who received GTN preoperatively are as follows:

$$k = 0.236 \times (1 - 0.0274 \times [\text{age} - 70]) \times (1 + 0.0194 \times (\text{weight} - 70))\ \text{min}^{-1}$$

$$m = 62.0 \cdot (1 + 0.0274 \times [\text{age} - 70]).$$

TABLE 2. Demographic and Clinical Characteristics of Elderly (> 70 yr) *versus* Young (< 70 yr) Subjects Given Glyceryl Trinitrate

	Elderly (n = 23)	Young (n = 16)	*P* Value
Age (yr)*	75	60	<0.001
Males (%)	78	44	0.03
Weight (kg)*	75	69	NS
β blockers (%)	26	38	NS
Ca blockers (%)	22	31	NS
Nitrates (%)	9	13	NS
Hx HTCVD (%)	70	75	NS
Hx angina (%)	17	6	NS
Hx MI (%)	13	13	NS

NS = not significant.
* Mean values.

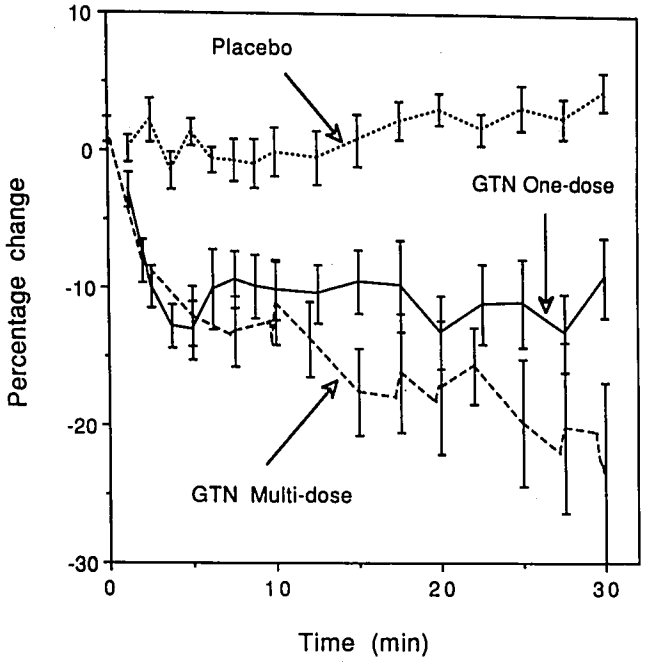

FIG. 1. The data for preoperative systolic arterial blood pressure *versus* time are presented for patients who received infusions of placebo (dotted line), and one dose (solid line) and multiple doses (dashed line) of nitroglycerin. Mean values ± 1 SEM are shown.

TABLE 3. Stepwise Selection of Variables*

Stage	Effect Tested	LLD	*P* Value
1	correlation of k and m†	−54.3	<0.005
2	1 + age effect on k	−3.6	<0.1
	1 + age effect on m	−7.5	<0.025
	1 + weight effect on k†	−12.3	<0.005
	1 + weight effect on m	−8.9	<0.005
	1 + gender effect on k	−0.9	NS
	1 + gender effect on m	−6.0	<0.025
	1 + volume status effect on k	−2.9	<0.10
	1 + volume status effect on m	−0.2	NS
	1 + nitrate exposure effect on k	−0.5	NS
	1 + nitrate exposure effect on m	−1.5	NS
3	2 + age effect on k	−5.8	<0.025
	2 + age effect on m†	−8.1	<0.005
	2 + weight effect on m	−1.5	NS
	2 + gender effect on m	−1.2	NS
	2 + volume status effect on k	−3.6	<0.10
4	3 + age effect on k†	−12.4	<0.005
	3 + volume status effect on k	−2.3	<0.15
5	4 + volume status effect on k	−0.9	NS
6	4 same effect of age on k and m†‡	+0.2	NS

LLD = decrease in log likelihood ratio. A decrease of more than 4 is statistically significant.
* Definitions of models and parameters are given in Appendix 2.
† The model selected at each stage and used in subsequent stage(s) indicated by "2+," "3+," or "4+" notations. Stage 6 includes variables selected in stages 1, 2, 3, and 4. All unselected variables with LLD decreases of ≥2 at any stage are retained as candidates for selection at the next stage.
‡ The variables selected for the final model. Although stage 6 provides no significant improvement in model fit, it is simpler than the model of stage 4, and therefore was selected as the final model.

The correlation between k and m is -0.865. The interindividual variations (coefficients of variation) of k and m are 176% and 115%, respectively, and the intraindividual variability (standard deviation) of SAP is 7.91 mmHg. The constant 70 in the model was chosen as the approximate median age and weight of the population; it does not influence the model fit.

Model parameters and fit were essentially identical with and without the data from the 13 patients who received the stepwise increasing infusion of GTN, thus confirming our findings of a significant effect of age on preoperative GTN responsiveness. Plots of the weighted residuals of all the data *versus* the SAP predicted by the model showed random variation above and below zero, suggesting the absence of a systematic model misfit (fig. 2). In figure 3, plots of SAP *versus* time are summarized for patients receiving a constant infusion of GTN: the dotted line is a locally smoothed value of the data (moving average) and the solid line is the SAP predicted with the parameters of the model. The locally smoothed value underestimates the SAP response at times after 5 min because it does not take into consideration the effect of patients who were withdrawn from the study because of hypotension. The model estimates the effects of the patients who were withdrawn because of hypotension and includes these effects in its overall prediction of the SAP response. The model predicts that patients in their 70s who receive GTN will average a twofold greater decrease in SAP than patients in their 50s (fig. 4). We chose SAP, and not mean arterial pressure (MAP), as the principal variable to model in our analysis because SAP is the blood pressure parameter usually recorded by anesthesiologists. However, we also measured MAP in all patients and found a close correlation between it and SAP ($r^2 = 0.85$), as expected.

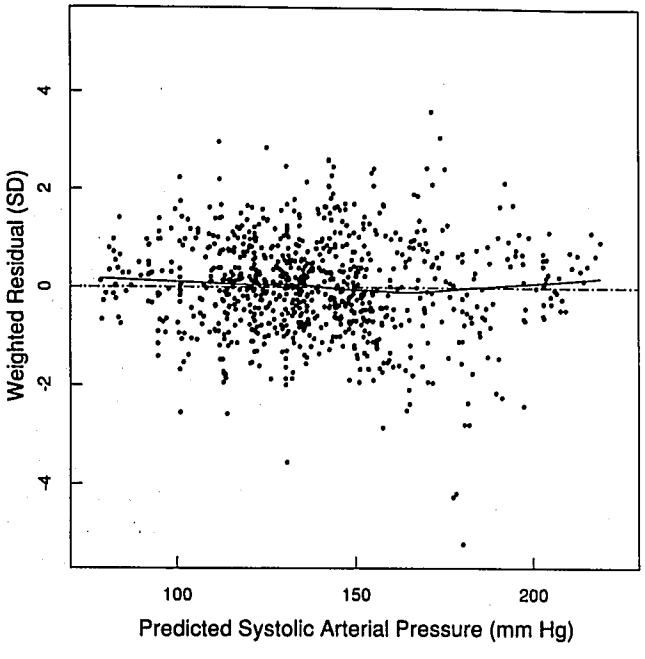

FIG. 2. The data for weighted residuals (WRES) from the fit of the final model (table 3, stage 6) *versus* predicted systolic blood pressures are presented for patients given nitroglycerin preoperatively. The dotted line is at zero; the solid line is a locally smoothed average (moving average) of the residuals. The random and approximately equal distribution of residuals above and below the zero line help confirm the adequacy of the final model.

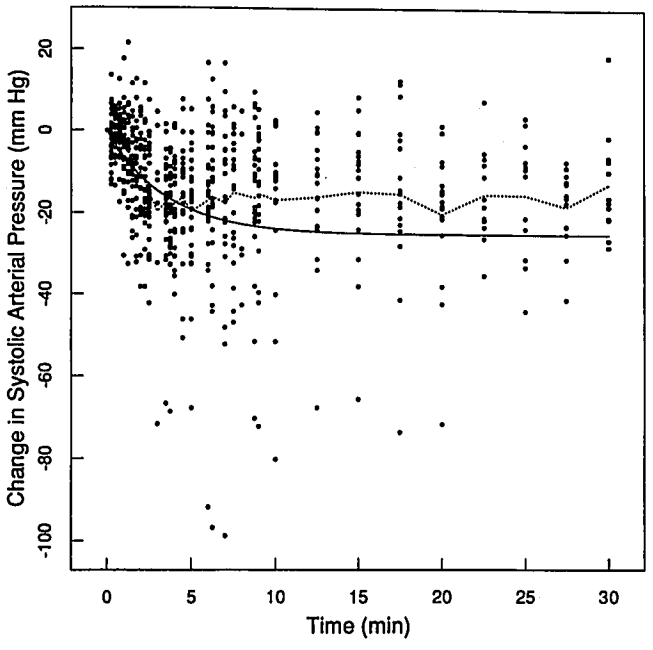

FIG. 3. Predicted (solid line) systolic arterial pressures *versus* time for a patient (age 68 yr, weight 74 kg, *i.e.*, mean age and weight of the study population) receiving a constant preoperative infusion of GTN, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, are presented. All individual points for all patients in the single dose protocol are also shown. The dotted line is a locally smoothed average of the individual points and, therefore, at later times, includes only data from patients without hypotension.

INTRAOPERATIVE STUDIES

Infusion of placebo had no significant effect on SAP or heart rate. However, the variability of SAP within subjects during the intraoperative phase was twofold greater than during the preoperative phase. Three patients were withdrawn from the study before the intraoperative phase: one because of severe hypotension encountered in the preoperative phase, one because treatment with intravenous GTN was started during induction of anesthesia to treat myocardial ischemia, and one because of malfunction of the infusion pump. In the other patients, hemodynamic values preceding the intraoperative infusion

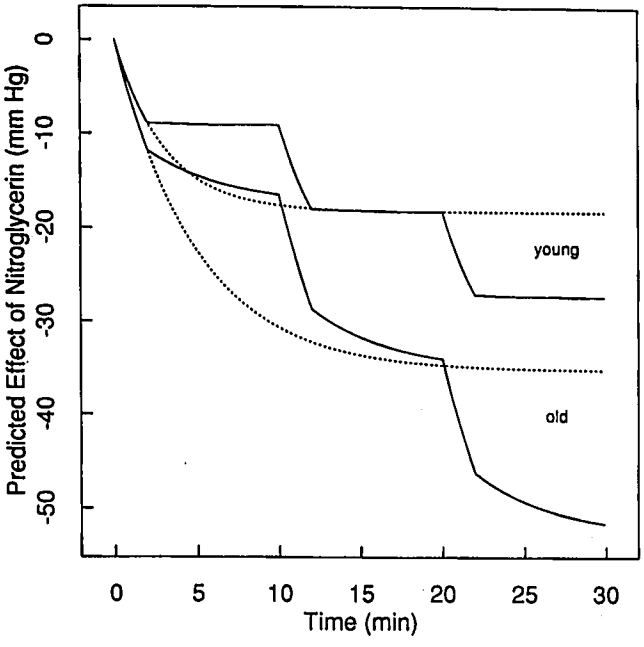

FIG. 4. Predicted systolic blood pressure *versus* time for young patient (age 55 yr) and old patient (age 75 yr) given nitroglycerin preoperatively according to our single continuous dose (dotted line) or multiple stepwise doses (solid line) protocol.

were quite comparable to those recorded before the preoperative infusion, except that SAP was 16 mmHg lower (table 4).

Intraoperatively, GTN consistently reduced SAP but did not change heart rate significantly. In 11 of 21 patients older than 70 yr of age and 2 of 15 younger patients, the GTN infusion was stopped because hypotension developed, but no patient had complications and all data were used in the analysis. Nine of the 13 patients who had hypotension during the preoperative GTN infusion also had it during the intraoperative infusion.

However, our model, which assumed that the preoperative and intraoperative response to GTN were related (*i.e.*, allowing ω_{13} and ω_{24} to be nonzero), fit the data only marginally better ($P \sim 0.05$) than the simpler model, which assumed no relation (see Appendix 2 for definition of models and parameters). In other words, knowing a patient's preoperative response to GTN had no significant value for the prediction of his or her intraoperative response. Moreover, when the intraoperative data were modeled independently of the preoperative data, no effect of age on k or m was discernible.

Arterial Concentrations of GTN and Metabolites

The plasma concentrations of GTN and its dinitrate metabolites were determined in 382 arterial blood samples (64% of the total samples we anticipated). Two hundred sixteen samples were not obtained because studies were stopped before their scheduled completion, usually because the patient became hypotensive. Large differences in concentrations between patients and frequent fluctuations in concentrations within patients were observed; therefore, no statistically significant differences between age groups or study periods emerged (table 5). Moreover, we found no consistent relationship between changes in arterial concentrations of GTN or its metabolites and arterial blood pressure.

Discussion

Preoperative Studies

We studied the blood pressure response to intravenous GTN in awake and anesthetized patients because this response is likely to influence the therapeutic benefit of GTN critically.

In a randomized prospective trial, Jugdutt and Warnica reduced acute myocardial infarct size and the incidence of left ventricular failure and death by administering 45 ± 34 μg/min (± standard deviation) intravenous GTN

TABLE 4. Hemodynamics and Anesthetic Conditions

	Preceding Preoperative Study	Preceding Intraoperative Study	N	P
SAP (mmHg)	154	138	49	<0.01
DAP (mmHg)	65	67	49	NS
MAP (mmHg)	95	91	49	0.08
MPAP (mmHg)	19	21	9	NS
PCWP (mmHg)	15	15	8	NS
CVP (mmHg)	10	11	10	NS
CO (l/min)	5.0	5.0	8	NS
SVR (dyne·s·cm^{-5})	1,343	1,395	7	NS
ISO (mmHg)	N/A	0.6	49	N/A
CO_2 (mmHg)	41	37	44	<0.01
N_2O (mmHg)	N/A	50	47	N/A
Fent (μg/kg)	N/A	3.9	49	N/A
Fluid (ml/kg)	12	34	48	<0.01

SAP, DAP, MAP = systolic, diastolic, and mean arterial pressures, respectively; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CO = cardiac output; SVR = systemic vascular resistance; ISO = end-tidal isoflurane concentration; CO_2 = arterial carbon dioxide tension; N_2O = end-tidal nitrous oxide concentration; FENT = intravenous fentanyl administered during anesthetic preceding intraoperative GTN infusion; FLUID = fluid administered from midnight on the day of study to preoperative or intraoperative infusion of GTN; N = number of patients with available data immediately preceding the preoperative and intraoperative infusions (For instance, 48 of 53 patients had SAP data available: 3 patients were not studied intraoperatively and one patient [from the placebo group] was not studied preoperatively to prevent a delay in the start of surgery. Nine patients had pulmonary artery catheters and one had a central venous catheter placed prior to induction of anesthesia); P = the paired *t* test value, which if greater than 0.1 is shown as NS (nonsignificant); N/A = not applicable.

TABLE 5. Mean Arterial Concentrations of Nitroglycerin during Constant Infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$

Preoperative Plasma Concentrations				
Time (min)	Young	n	Old	n
5	27.1 ± 7.2	9	19.7 ± 13.0	12
7.5	33.2 ± 10.0	9	8.6 ± 2.3	10
10	13.7 ± 4.4	9	29.9 ± 24.4	8
15	32.0 ± 13.5	9	28.0 ± 22.0	8
Intraoperative Plasma Concentrations				
Time (min)	Young	n	Old	n
5	50.3 ± 22.9	8	23.8 ± 11.9	8
7.5	27.5 ± 14.7	7	18.7 ± 8.8	8
10	10.5 ± 2.2	8	19.0 ± 9.8	8
15	13.8 ± 4.4	4	16.6 ± 9.4	7

Values are mean ± SEM. Comparable fluctuations in the plasma concentrations were also seen during the stepwise increasing infusions, therefore, these data are not shown.

Young = patients younger than 70 yr, n = number of plasma samples analyzed; Old = patients 70 yr of age or older.

(compared with our average dose of 44 ± 4 $\mu g/min$).[11] Infarct size decreased significantly less when GTN was administered 4 or more hours after the onset of infarction or its administration induced hypotension (*i.e.*, an MAP < 80 mmHg [14 of 154 patients, ages not given]). In a canine model of acute infarction, GTN increased collateral blood flow and myocardial salvage unless it reduced MAP to < 83 mmHg.[12] In our current study, 10 of our 23 patients older than 70 yr of age given GTN preoperatively (2 given 0.25, 6 given 0.5, and 2 given 0.75 $\mu g \cdot kg^{-1} \cdot min^{-1}$) became hypotensive (averaging a 30% decrease in MAP to 66 ± 13 mmHg), whereas only 3 of 16 younger patients (1 given 0.25 and 2 given 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) became hypotensive (24% decrease in MAP to 68 ± 8 mmHg). In our preoperative model, age was a significant determinant of the effect of GTN on SAP (table 3). Thus, if nonanesthetized elderly patients are given the same dose of GTN as nonanesthetized younger patients, the elderly are more likely to experience hypotension and may be less likely to derive any therapeutic benefit. Therefore, we recommend anticipating a lower GTN requirement initially in elderly patients to permit safer titration.

Previous studies of the effects on the pharmacodynamics of GTN in elderly patients provide conflicting results. Gascho *et al.* found that nasal administration of 0.8 mg GTN to 50 healthy subjects (aged 21–78 yr) produced less venous distension in patients older than 60 yr than in younger patients (11 ± 5% *vs.* 16 ± 6% increase in venous volume of the forearm).[13] In contrast, Eicher *et al.* found no age-related changes (patients aged 19–74 yr) in venous responsiveness of a dorsal hand vein to nitroglycerin.[14] Marchionni *et al.* studied 24 patients (12 younger than 65 yr and 12 older than 75 yr) with acute myocardial infarction and left ventricular failure.[15] Hemodynamic values before GTN administration were comparable in the two groups, including pulmonary artery wedge pressure greater than 25 mmHg. However, older patients reached the hemodynamic end point (a 5–10% decrease in MAP) at a significantly lower GTN infusion rate (0.7 ± 0.1 *vs.* 1.7 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in younger patients; $P < 0.01$). Moreover, pulmonary artery wedge pressure at this end point was almost twofold lower in older patients (51 ± 5% reduction *vs.* 29 ± 4%; $P < 0.005$). Unlike in our study, Marchionni *et al.* evaluated only patients with left ventricular failure and did not explore the potentially confounding effects of weight and gender on the pharmacodynamics of GTN.[15]

The net effect of GTN on SAP will depend on the amount of active drug and/or metabolites reaching the site of action, their effects at the site of action, and circulatory reflexes in response to these effects. Unfortunately, standard (table 5), semiparametric, and population-based pharmacokinetic data analysis did not determine whether our elderly patients had significantly different arterial concentrations of GTN or its dinitrate metabolites than younger patients[16–18] because, like other investigators, we found large interpatient and intrapatient differences in plasma concentrations of these nitrates during apparently steady state conditions.[19–22] Plasma nitrate concentrations probably vary so dramatically because only approximately 1% of the total nitroglycerin and its metabolites is present in the plasma, with the balance being tissue bound.[19] Therefore, small changes in tissue binding may produce large changes in plasma concentrations and obscure efforts to characterize the pharmacokinetics of the drug, including age-related effects. However, an age-related difference in the effect of GTN at the active site is likely, according to the results of Gascho *et al.*, indicating decreased venous distensibility in elderly patients.[13] If this difference applied to our patients, it must have been overshadowed by decreased circulatory compensation. Because left ventricular and arterial compliance are lower in elderly patients than in younger patients, significant reductions in cardiac output and SAP are likely to occur in response to decreased venous return.[6]

Patient weight was a second significant determinant of the preoperative SAP response to GTN, even though we administered GTN on a per-kilogram basis. However, intravascular volume does not increase in direct proportion to body weight. Administration of GTN based on body surface area might have made it easier to examine the influence of patient size on GTN response, but such dosing rarely is used in acute care medicine.

Intraoperative Studies

The impact of anesthesia and surgery on the pharmacodynamics of most vasoactive drugs is poorly defined. Unfortunately, this remains the case for intravenous GTN. Our results indicate no consistent relationship between the preoperative and intraoperative effects of GTN on blood pressure. Why did this occur? Three possible explanations are suggested by our data.

First, despite our efforts to maintain anesthetic and surgical parameters as stable as possible (a high-dose narcotic technique was not a clinically acceptable alternative), we observed a twofold greater variability in systolic blood pressure intraoperatively than preoperatively. Perhaps this variability was of sufficient magnitude to obscure the relationship (if any) between intraoperative blood pressure response to GTN and other variables, such as age or the preoperative blood pressure response. Another way of viewing this explanation is to consider the possibility that the major factors controlling intraoperative responsiveness to GTN (perhaps surgical stress, catecholamine levels, cardiovascular reserves) are not part of our model and therefore act as noise obscuring the small "signal" associated with age or whatever persistent physiologic adaptation is measured by the preoperative GTN response.

A second explanation is that anesthesia may have altered the reflex response to GTN. This explanation is suggested by the fact that comparable decreases in SAP occurred preoperatively and intraoperatively, but heart rate increased significantly only before surgery. Isoflurane depresses the baroreceptor reflex and therefore could have been responsible for this finding.[23] If this explanation holds, then preoperative response does not predict intraoperative response because the physiologic mechanisms responsible for each are relatively distinct and, presumably, poorly correlated.

Finally, like GTN, isoflurane dilates vascular smooth muscle and, by this mechanism, may have obscured the effects of GTN partially.

For whatever reason, the immediate preoperative effect of GTN on blood pressure is an unreliable guide to its effect during anesthesia and surgery. Therefore, preoperative testing of the blood pressure response to GTN is of no practical value in determining intraoperative dose.

Study Limitations

Our study has some significant limitations. First, we have not studied many elderly women; thus, we have not fully defined the possible effects of gender. Second, our mathematical expression for the effect of GTN on SAP assumes a continuum of responses, when, in fact, some patients have a significant decrease in SAP and others none at all. Although the advantages of constructing such a mathematical model are numerous and include the opportunity to test for the independence of influencing variables, our model has limited value in predicting the SAP response in an individual patient. Third, because the patients who had the greatest decrease in SAP with GTN were studied for the shortest time (studies were discontinued because of hypotension), our estimates of their expected dose response are less precise than our estimates for the other patients. Fourth, we used only clinically indicated monitors, and, therefore, did not place pulmonary artery catheters in most of our patients. Thus, we have not adequately defined the effects of GTN on cardiac output or systemic vascular resistance.

Finally, the effect of GTN in our patients likely was confounded by other drug therapy, such as previously administered nitrates and β-blockers. Although nitrate therapy was discontinued at least 8 h before the study began (except in two patients in whom the last dose inadvertently was administered 100 min before the study), significant levels of metabolites may have been present. Perhaps the 8 h of abstinence and/or the small number of patients exposed to nitrates before study prevented us from detecting any apparent tolerance to GTN. β-Blockers were administered until the time of study, but in too few patients to allow their effects to be discerned. Morphine and diazepam were administered before the study and may have altered the effects of GTN, but these drugs were given in approximately equal doses to young and old patients. It is interesting that some elderly patients are more sensitive to the sedative effects of diazepam[24] and analgesic effects of morphine[25]; thus, it is theoretically possible that part of the age-dependent effect of GTN on blood pressure resulted from a more profound effect of our premedications on elderly patients. However, we found no evidence of greater sedation in our elderly patients. For instance, Pa_{CO_2s} immediately before the preoperative GTN infusion were virtually identical in the two age groups (41.3 ± 5.5 mmHg in patients older than 70 yr *vs.* 41.4 ± 5.4 mmHg in patients younger than 70 yr), as were the SAP responses to the operating room setting (22 ± 29 mmHg *vs.* 22 ± 24 mmHg increase in SAP compared with the ward SAP). Thus, we doubt that our elderly patients were significantly more sedated by the premedication than our younger patients. Moreover, morphine and diazepam are administered quite commonly in acute care settings in which GTN is required.

We conclude the following: 1) in the absence of the effects of anesthesia and surgery, elderly patients have a more pronounced blood pressure response to intravenous nitroglycerin than do younger patients; 2) variations in arterial plasma concentrations of nitroglycerin and its metabolites at steady state are too large to detect significant pharmacokinetic differences between elderly and

young patients; and 3) the preoperative blood pressure responsiveness to nitroglycerin is not a reliable predictor of intraoperative responsiveness.

The authors thank Winifred von Ehrenburg, Celeste Mangold, and Irene Lam for assistance in preparing this manuscript, and Marianne T. Cahalan, R.N., Maile Ota, R.N., Patricia J. Radle, R.N., Pamela J. Colton, R.N., and Robert A. Price for technical assistance.

References

1. Thadani U, Whitsett T: Relationship of pharmacokinetic and pharmacodynamic properties of the organic nitrates. Clin Pharmacokinet 15:32–43, 1988
2. Fung HL: Pharmacokinetics and pharmacodynamics of organic nitrates. Am J Cardiol 60:4H–9H, 1987
3. May DC, Popma JJ, Black WH, Schaefer S, Lee HR, Levine BD, Hillis LD: In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. N Engl J Med 317:805–809, 1987
4. Fung HL, Blei A, Chong S: Interpretation of nitrate plasma concentrations: Effect of cardiac output on nitroglycerin pharmacokinetics in experimental animals. Eur Heart J 9(suppl A):39–43, 1988
5. Fleisch JH, Hooker CS: The relationship between age and relaxation of vascular smooth muscle in the rabbit and rat. Circ Res 38:243–249, 1976
6. Lakatta EG: Alterations in the cardiovascular system that occur in advanced age. Fed Proc 38:163–167, 1979
7. White NK, Edwards JE, Dry TJ: The relationship of the degree of coronary atherosclerosis with age in men. Circulation 1:645–649, 1950
8. Lee FW, Watari N, Rigod J, Benet LZ: Simultaneous determination of nitroglycerin and its dinitrate metabolites by capillary gas chromatography with electron-capture detection. J Chromatogr 426:259–266, 1988
9. Beal SL, Sheiner LB: Methodology of population pharmacokinetics, Drug Fate and Metabolism. Edited by Garrett ER, Hirtz JL. New York, Marcel Dekker, 1985, pp 135–183
10. Cox DR, Hinkley DV: Theoretical Statistics. London, Chapman and Hall, 1974, pp 135–184
11. Jugdutt BI, Warnica JW: Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications: Effect of timing, dosage, and infarct location. Circulation 78:906–919, 1988
12. Jugdutt BI: Myocardial salvage by intravenous nitroglycerin in conscious dogs: Loss of beneficial effect with marked nitroglycerin-induced hypotension. Circulation 68:673–684, 1983
13. Gascho J, Fanelli C, Zelis R: Aging reduces venous distensibility and the venodilatory response to nitroglycerin in normal subjects. Am J Cardiol 63:1267–1270, 1989
14. Eichler HG, Hiremath A, Katzir D, Blaschke TF, Hoffman BB: Absence of age-related changes in venous responsiveness to nitroglycerin in vivo in humans. Clin Pharmacol Ther 42:521–524, 1987
15. Marchionni N, Schneeweiss A, Di BM, Ferrucci L, Moschi G, Salani B, Paoletti M, Burgisser C, Fumagalli S: Age-related hemodynamic effects of intravenous nitroglycerin for acute myocardial infarction and left ventricular failure. Am J Cardiol 61:81E–83E, 1988
16. Verotta D, Sheiner LB: Comparing predictor-responses series by comparing their regression curves. Am J Physiol, in press
17. Guardabasso V, Rodbard D, Munson PJ: A model-free approach to estimation of relative potency in dose-response curve analysis. Am J Physiol 252:E357–E364, 1987
18. Lawton WH, Sylvestre A, Maggio MS: Self modeling nonlinear regression. Technometrics 14:513–532, 1972
19. McNiff EF, Yacobi A, Young-Chang FM, Golden LH, Goldfarb LH, Fung HL: Nitroglycerin pharmacokinetics after intravenous infusions in normal subjects. J Pharm Sci 70:1054–1058, 1981
20. Nakashima E, Rigod JF, Lin ET, Benet LZ: Pharmacokinetics of nitroglycerin and its dinitrate metabolites over a thirtyfold range of oral doses. Clin Pharmacol Ther 47:592–598, 1990
21. Noonan PK, Benet LZ: Incomplete and delayed bioavailability of sublingual nitroglycerin. Am J Cardiol 55:184–187, 1985
22. Parker JO, Fung HL: Transdermal nitroglycerin in angina pectoris. Am J Cardiol 54:471–476, 1984
23. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP: Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. ANESTHESIOLOGY 60:173–179, 1984
24. Reidenberg MM, Levy M, Warner H, Coutinho CB, Schwartz MA, Yu G, Cheripko J: Relationship between diazepam dose, plasma level, age, and central nervous system depression. Clin Pharmacol Ther 23:371–374, 1978
25. Kaiko RF: Age and morphine analgesia in cancer patients with postoperative pain. Clin Pharmacol Ther 28:823–826, 1980

Appendix 1: Assay of Plasma Nitroglycerin and Dinitrate Metabolites

We used the technique described by Lee *et al.*,[8] with the following modifications.

Chemicals and Reagents

We used GTN (Tridil®) from DuPont Pharmaceuticals, Inc. (Wilmington, DE). Dinitrate metabolites were a gift from Dr. L. Z. Benet. The 2,6-dinitrotoluene was from Aldrich Chemicals (Milwaukee, WI), and pentane, methyl-t-butyl ether, and butyl acetate were from Burdick & Jackson (Muskegon, MI).

Instruments

A Hewlett-Packard 5890A Gas Chromatograph with a ^{63}Ni electron capture detector (Avondale, PA), J & W on-column injector (Folsom, CA), and Hewlett-Packard 3392A integrator was used. The temperature of the gas chromatograph oven was maintained at 92° C for 8 min, then programmed to 120° C at a rate of 3° C/min, followed by a second step to 260° C at a rate of 50° C/min, which was maintained for 5 min. The detector make-up flow was nitrogen at 45 ml/min; the carrier was hydrogen at 15 ml/min; and the purge was 60 ml/min. We used an HP-1 fused silica column (25 m × 0.32 mm ID and 1-μm film thickness) from Hewlett-Packard.

Sample Preparation

All plasma samples (1 ml) were spiked with the internal standard (0.5 ng 2–6,dinitrotoluene), extracted (5 min twice on a mechanical rotor at 25 rotation/min) with 10 ml of pentane and methyl t-butyl ether solvent (80:20, volume/volume), and then centrifuged at 1500 × g for 10 min. The organic phase was dried under nitrogen and resuspended in 50 μl butyl acetate. We injected 0.1–1 μl of the samples into the gas chromatograph

using an on-column gas-tight injector syringe with a 19-cm fused silica needle. Spiked controls and calibration curve sets were prepared with blank plasma (Super Plasma, Biological Specialty, Chalfont, PA).

Standard Curves

Known amounts of GTN and metabolites were prepared in aqueous solutions and added to tubes with 1 ml of blank plasma to yield standard samples (0.4, 4, and 12.5 ng/ml) and calibration points (0, 0.1, 0.3, 0.5, 0.75, 1, 3, 5, 7.5, 10, and 15 ng/ml). As described by Lee *et al.*,[8] we used a two-slope calibration curve with a break point at 1 ng/ml. In the low concentration range (0–1 ng/ml), the best fit was a linear curve. In the high concentration range (1–15 ng/ml), the best fit was a polynomial of the second order. The coefficient of variation for intraday and interday variability in plasma level determinations for GTN ranged from 2.3% to 5.6% and for its dinitrate metabolites from 1.9% to 12.5%, with the use of controls at low (0.4 ng/ml), medium (4 ng/ml), and high (12.5 ng/ml) concentration ranges.

Appendix 2: Mathematical Modeling

The population model we developed for the preoperative SAP response to an infusion (I) of placebo or GTN assumes that the kinetics can be described as linearly related to a monoexponential accumulation of drug effect:

$$SAP = SAP_0 - I \times m \times (1 - e^{-k \times t})$$

where SAP_0 is the mean SAP during the 2 min preceding the start of the infusion, m is a proportionality constant linking I and SAP, and k is the monoexponential rate constant. Both m and k are assumed to vary among patients. An initial hypothesis that assumed no correlation between m and k was evaluated by comparing a model fit with and without such correlation. Thereafter, the effects of influencing variables on k and m were assessed by stepwise addition of variables to the models, with evaluation of the improvement in overall model fit after each step with the asymptotic chi-square distribution of the log likelihood ratio as the criterion. The data analysis for patients receiving the constant GTN infusion was conducted with and without the additional data from the patients who received the stepwise increasing infusion to determine whether the additional data altered the results.

The same basic model was used to analyze the intraoperative data, except that the covariance (if any) between preoperative and intraoperative individual values of m and k also is modeled:

$$SAP_{ijk} = SAP_{0ij} - I_{ij} \times m_{ij} \times (1 - e^{-k_{ij} \times t_{ijk}}) + \epsilon ijk$$

where SAP_{ijk} is the SAP observed in patient i, in trial j (j = 1 for preoperative, and j = 2 for intraoperative), at time t_{ijk}; SAP_{0ij} is the baseline (immediately before the infusion) SAP for patient i in trial j; I_{ij} is the infusion rate; m_{ij} is the corresponding slope of the "dose" response curve (a parameter estimated by the model); k_{ij} is the rate constant (a parameter also estimated by the model); and ϵ_{ijk} are independent random errors, with zero mean and variance s^2. Two of the parameters are further modeled:

$$m_{ij} = m_j + \eta_{i,2(j-1)+1}$$

$$k_{ij} = k_j + \eta_{i,2j}$$

where η indicates random interindividual differences. $\eta_{i,1}$ is the difference between S_{i1} and S_1 (*i.e.*, the difference between the slope of the dose response curve for the i^{th} individual in the preoperative trial [s_{i1}] and the preoperative population mean slope [S_1]). Likewise, $\eta_{i,2}$ is the individual difference for the preoperative rate constant. The individual vectors $\eta_i = (\eta_i, 1, \ldots)'$ are independent, but the elements of each may be correlated. If $\Omega = \{\omega_{lm}\}$ denotes the covariance matrix of η, then ω_{11} (ω_{33}) is the interindividual variance of the preoperative (intraoperative) slopes, ω_{22} (ω_{44}) is the interindividual variance of preoperative (intraoperative) rate constants, and $\omega_{12} = \omega_{21}$ ($\omega_{34} = \omega_{43}$) is the covariance between the preoperative (intraoperative) slope and rate constant. The elements ω_{13} and ω_{24} express the covariance between the preoperative and intraoperative slope and rate constant, respectively, within the same patient. If the corresponding correlations are large, the preoperative response of a patient is likely to predict the intraoperative response.