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Norepinephrine kinetics and dynamics in septic shock and trauma patients

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Background. There is considerable variability in the inter-patient response to norepinephrine. Pharmacokinetic studies of dopamine infusion in volunteers and in patients have also shown large variability. The purpose of this study was to define the pharmacokinetics of norepinephrine in septic shock and trauma patients.

Methods. After Ethical Committee approval and written informed family consent, 12 patients with septic shock and 11 trauma patients requiring norepinephrine infusion were studied. Norepinephrine dose was increased in three successive steps of 0.1 mg kg^{-1} min^{-1} at 15-min intervals (20% maximum allowed increase in arterial pressure). Arterial blood was sampled before and at 0.5, 13, and 15 min after each infusion rate change and 30 s, 1, 2, 5, 10, and 15 min after return to baseline dosing. Norepinephrine was assayed by HPLC. The pharmacokinetics were modelled using NONMEM (one-compartment model). The effects of group, body weight (BW), gender and SAPS II (Simplified Acute Physiology Score II) [Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *J Am Med Assoc* 1993; 270: 2957–63] patients score on clearance (CL) and volume of distribution (V) were tested.

Results. Group, gender, and BW did not influence CL or V. CL was negatively related to SAPS II. CL and $T_{1/2}$ varied from 3 litre min^{-1} and 2 min, respectively, when SAPS II=20 to 0.9 litre min^{-1} and 6.8 min when SAPS II=60.

Conclusion. In trauma patients and in septic shock patients, norepinephrine clearance is negatively related to SAPS II.

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Norepinephrine infusion is used routinely to support arterial pressure and organ function in critically ill patients. Clinical experience suggests there is considerable inter-patient variability in response to norepinephrine infusions. Multiple factors, for example age, renal function, hepatic function, may influence the response to norepinephrine. Free radicals, produced in large quantity in septic shock and trauma, may interact with catecholamines and decrease their concentration.[1] Thus, the pressor response, and other effects such as the modulation of cytokines release,[2 3] may vary with the pharmacokinetics of norepinephrine. Few clinical studies have addressed the variability of the effects of norepinephrine.[4–6] Studies with dopamine in volunteers[7] and in patients,[6] and with dobutamine in critically ill surgical patients[8] have shown both intra- and inter-subject variability in infusion rate and serum concentrations. This makes standard pharmacokinetic modelling of less utility than for other drugs. Similarly, norepinephrine plasma concentrations were poorly related to the infusion rate in patients with head trauma.[6] Norepinephrine is rapidly eliminated from the blood (half-life is 2–2.5 min). However, when norepinephrine is administered at a dose 10^3–10^6 times higher than the natural spill-over (the fraction of synthesis not metabolized locally), it is conceivable that the metabolic pathways become saturated, leading to non-linear pharmacokinetics. Norepinephrine's pharmacodynamic effect depends on vascular tone, which has been reported to be impaired in trauma[9] and septic patients.[10] Therefore, the variability in the clinical response to norepinephrine may depend on both pharmacokinetic and pharmacodynamic factors.

The purpose of this study was to determine the pharmacokinetics and pharmacodynamics of norepinephrine

in patients with septic shock and in trauma patients. Our hypothesis was that a pharmacokinetic–pharmacodynamic (PK–PD) model of norepinephrine could be used to define doses of the drug that would be required to obtain specific plasma concentrations in septic shock and in trauma. Similarly, we expected that one or several simple covariates might explain part of the variability in PK–PD.

Patients and methods

After Ethics Committee approval and written informed consent, 23 patients (12 septic shock patients and 11 trauma patients) requiring an infusion of norepinephrine to support arterial pressure were enrolled. These patients were all sedated with midazolam and sufentanil infused at a constant rate, and mechanically ventilated. Patients were included within 24 h of starting catecholamines. Exclusion criteria were as follows: (1) age under 18 yr; (2) pregnancy; (3) history of coronary disease, cardiac failure, cardiac rhythm trouble. The criteria for inclusion in the group with sepsis syndrome have been reported previously[11] and include fever (temperature >38.3°C) or hypothermia (temperature <35.5°C), tachycardia (>90 beats min^{-1}), tachypnoea (>20 breaths min^{-1}), clinical suspicion of infection, and at least one of the following: hypoxaemia (Pa_{O_2}<9.6 kPa on room air or Pa_{O_2} (mm Hg)/FI_{O_2}<280), oliguria (urine output <30 ml or 0.5 ml kg^{-1} BW for 1 h), unexplained metabolic acidosis (or an elevated plasma lactate level), or a recent change in mental status. Multiple trauma patients were defined by an Injury Severity Score (ISS) >16.

On admission to ICU, monitoring included heart rate, invasive arterial pressure, oxygen saturation, ventilatory frequency, and temperature. Biologic variables (hepatic enzyme, renal function, haemoglobin, haemostasis) were also recorded.

We only considered septic shock and trauma patients that required a norepinephrine infusion within their first day, and patients were enrolled within 24 h of starting norepinephrine. Standards of care were not modified by the study. All patients were already treated with norepinephrine, which was administered through a central venous catheter. The patients were not receiving any other drugs. After an initial period of 60 min, the norepinephrine dose was increased by three successive steps of 0.1 mg kg^{-1} min^{-1}, at 15-min intervals (with a 20% maximum allowed increase in arterial pressure). The dose was then reduced to the initial level. Clinical and biological variables were measured before changing the norepinephrine rate, at t30 s (on the steep part of the concentration–time curve), t13 min, t15 min (when steady concentration was approached) for each of the three steps and at the end of the study. Additional sampling was performed in nine patients (five trauma and four septic) at t+30 s, t+1 min, t+2 min, t+5 min, t+10 min, and t+15 min after the dose was reset to its initial value.

Sampling and assay

Blood (5 ml) was sampled in tubes containing EGTA [ethylene glycol bis(2-aminoethyl ether)-*N*,*N*,*N*′*N*′-tetra acetic acid] and gluthatione. The tubes were immediately centrifuged at 4°C and plasma samples were stored at −20°C before assay. Norepinephrine concentration was measured, in plasma, using HPLC with coulometric detection.[12,13] Briefly, after the addition of the internal standard (dihydroxybenzoic acid, DHBA), the samples were extracted on alumina and 50 μl of the acidic extract was injected manually. The mobile phase consisted of a 90/10 (vol/vol) mixture of 0.03 M citric acid, 0.015 M Na_2HPO_4 buffer (pH 5.5) containing sodium octane-sulfonic acid 0.7 g $litre^{-1}$ and methanol. The mobile phase was set at a flow rate of 1 ml min^{-1}. The detector was a Coulochem (ESA model 5100A, Eurosep Cergy, St Christophe, France) with a 5011 analytical cell set at +0.03 and 0.30 V.

Statistical analysis

Normality was checked for continuous data using the Shapiro–Wilk test. Patient characteristics were compared between the two groups using the Student's *t*-test for continuous data and the χ^2 test for dichotomous data. An initial estimation of individual norepinephrine clearance was made by calculating the steady-state non-parametric clearance just before the first step increase in dosing (CL=dose/concentration). Data are reported as median (range) or mean (SD) where appropriate. Kinetic (concentration *vs* time) data and dynamic (mean arterial pressure *vs* time) data were fitted in a two-stage manner using mixed effect modelling with the software NONMEM (Version V, level 1).[14] Kinetics were modelled using a one-compartment model with first order elimination. In this case, the half-life ($T_{1/2}$) is directly proportional to the volume of distribution (V) and negatively proportional to clearance ($T_{1/2}$=0.693 V/Cl). We selected the one-compartment model after comparison with a two-compartment model using the Akaike criterion (AIC).[15] A random effect parameter was associated with clearance and volume to account for inter-individual variability. In a first step, Bayesian estimates of parameters (i.e. clearance and volume) obtained with a first NONMEM run were regressed on potential covariates, that is group, gender, BW, creatinine clearance, prothrombin time, and SAPS II score.[16] In a second step, a full model including the most pertinent covariates was constructed and reduced models were successively fitted. In addition, we compared individual clearances calculated with the non-parametric method and the NONMEM Bayesian estimates.

MAP *vs* norepinephrine concentration was modelled using the classic Emax model:

$$MAP = MAP_0 + \frac{MAP_{\mathrm{MAX}} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}},$$

where MAP_0 is the estimated basal arterial pressure in the absence of norepinephrine, MAP_{MAX} is the theoretical

Table 1 The study patients. Data are mean (range) or mean (SD) or number of patient (%). *P<0.01. †Cockroft formula

	Trauma (n=11)	Septic (n=12)
Gender		
Female	5	6
Male	6	6
Age (yr)	33 (19–66)	69 (53–88)*
Weight (kg)	69 (11)	69 (11)
SAPS II	30 (6)	42 (16)
Creatinine clearance (ml min^{-1})†	94 (34)	35 (17)*
Lactates (mmol litre^{-1})	1.8 (0.6)	2.7 (1.9)

maximum increase in MAP if norepinephrine was infused at an infinite dosage (in this case, the resulting maximum MAP would be MAP_0+MAP_{MAX}), C is NOR concentration, EC_{50} is the norepinephrine concentration leading to half MAP_{MAX} and γ is the Hill exponent. A random effect parameter was associated with MAP_0, MAP_{MAX}, EC_{50}, and γ to account for inter-individual variability. The PD model was fitted using the individual Bayesian estimates of PK parameters obtained with the most pertinent PK model, and the effect was considered to have occurred in the central compartment. The same stepwise procedure from the kinetic analysis was used to determine the best model according to potential covariates. For both PK and PD modelling we used the conditional estimation method with interaction and a heteroscedastic error model. The log likelihood ratio test was used for assessing the statistical significance between nested models. The inter-individual variability [95% confidence interval (95% CI) of the structural parameters] was assessed by log-likelihood profiling.

Results

Groups were similar in terms of gender, weight, and severity assessed with the (Simplified Acute Physiology Score II)[17] SAPS II score (Table 1). The septic group was significantly older and had a lower creatinine clearance than the trauma group (Table 1). The baseline dose received by the patients varied from 0.093 to 6.3 μg kg^{-1} min^{-1} with a median of 1.8 μg kg^{-1} min^{-1}. The initial observed norepinephrine concentration ranged from 0.99 to 186 mg ml^{-1} with a median of 16.2 mg ml^{-1}. No direct correlation between dose and concentration was observed. The initial regression step between Bayesian estimates of clearance obtained with the initial fitting and potential covariates showed that norepinephrine clearance was inversely related to SAPS II (Fig. 1). A full model incorporating group (trauma/septic), body weight and SAPS II score as predictive covariates for clearance was then constructed and successive reduced models were tested against this model. The best-reduced model was the model incorporating only the SAPS II score, confirming the prediction made by the initial regression step (Tables 2 and 3 and Fig. 2). None of the other covariates tested for inclusion in the model showed any statistically significant influence on clearance. Similarly, a model incorporating these previously mentioned potential covariates was built for volume of distribution prediction. However, none of these covariates showed any significant improvement of fitting. The terminal half-life varied from 2.0 min in the least severely ill patients (SAPS II=20) to 6.8 min in the most severe (SAPS II=66) (Table 3). The correlation between the two methods (non-parametric and Bayesian estimates) used for calculating clearance showed excellent agreement (Fig. 3). The assumption of linear kinetics is clearly supported by this correlation, and by

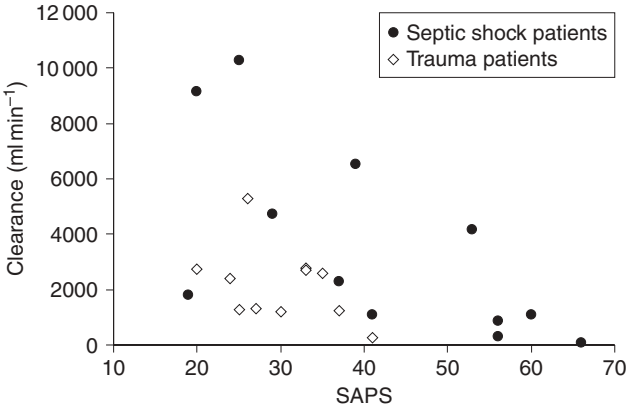

Fig 1 Correlation between clearance estimated by the initial regression model (without any covariate) and SAPS II.

Table 2 Model building and statistical significance. The best model is reduced model #3 (which only considers SAPS score as significant covariate). Goodness-of-fit is represented by the objective function (OF). A difference in OF of 6.63 (χ^2 with one degree of freedom, P<0.01) was considered significant

Full model	OF1=1328.411	
#1 with group (trauma/septic), weight, and SAPS score included		
Reduced models		
#2 Group not included	OF2=1329.203	P=0.373, OF2 *vs* OF1, 1 df
#3 Same as 2, weight not included	OF3=1331.781	P=0.108, OF3 *vs* OF2, 1 df
#4 Same as 2, SAPS score not included	OF4=1336.126	P=0.008, OF4 *vs* OF2, 1 df
#5 Fully reduced model	OF5=1338.992	P=0.007, OF5 *vs* OF2, 2 df

Table 3 Pharmacokinetic and pharmacodynamic parameters. CL=3000 ml min^{-1}, $T_{1/2}$=2.0 min if SAPS II=20, CL=2000 ml min^{-1}, $T_{1/2}$=3.1 min if SAPS II=30, CL=900 ml min^{-1}, $T_{1/2}$=6.8 min if SAPS II=66. Pharmacokinetic parameters are those obtained with the best-reduced model (model 3). Θ is the typical value of the population structural parameter estimates, ω^2 is the variance of the inter-individual variability parameter, and 95% CI is the 95% confidence interval of structural parameters obtained by profiling the log-likelihood

	Θ	ω^2	95% CI
CL (ml min^{-1})	59 600/SAPS	0.974	(38 800–91 000)/SAPS
V (ml)	8840	1.63	(3580–21 600)
MAP_0 (mm Hg)	71.0	0.0344	
MAP_{MAX} (mm Hg)	98.7	–	
EC_{50} (μg ml^{-1})	70.4	1.64	(62–420)
γ	1.80	–	

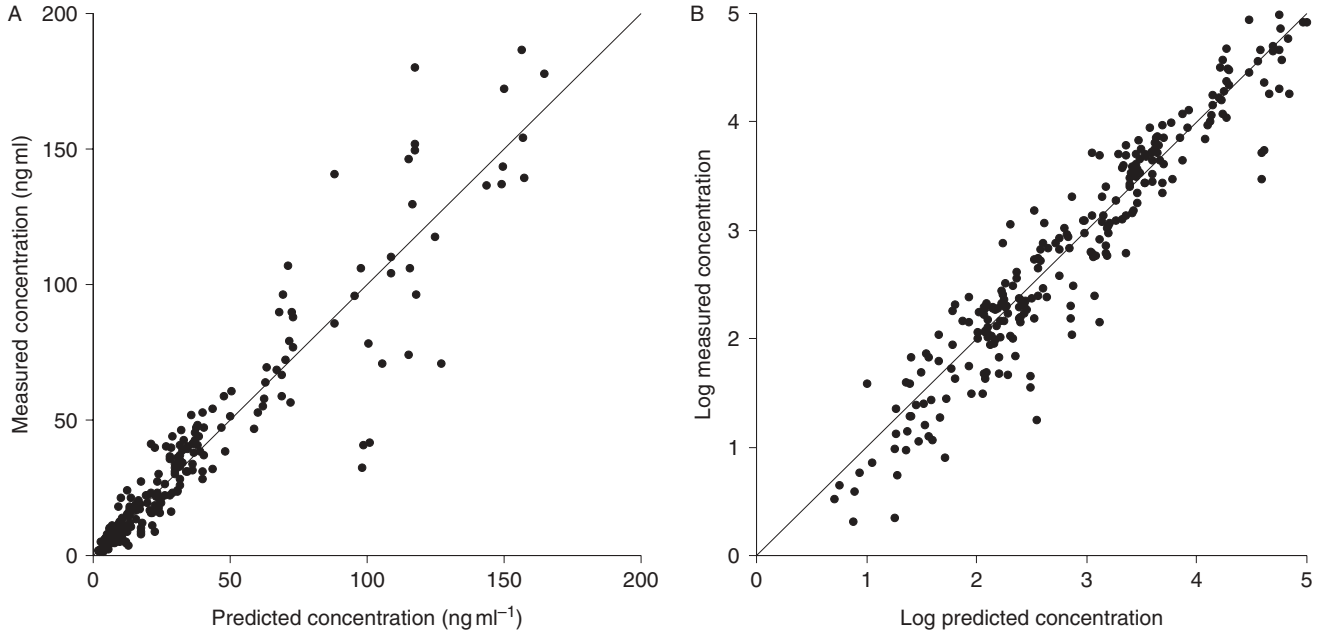

Fig 2 Goodness of fit. Measured *vs* predicted norepinephrine concentration. Data are represented on a Cartesian plot (A), and on a log–log plot (B).

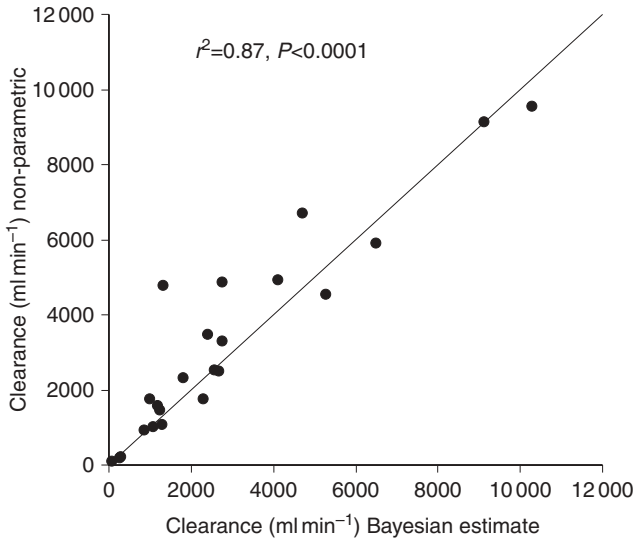

Fig 3 Correlation between clearance estimated by the one-compartment linear model and calculated by the non-parametric method.

the fact that fit was equally good at low and at high concentrations when the dose was increased (Fig. 2).

The overall basal MAP (MAP_0) was 71 (11) mm Hg. The pharmacodynamic data (MAP *vs* norepinephrine concentration and time) were adequately fitted by the E_{max} model. Random effects were significantly associated only with MAP_0 and MAP_{MAX}. Estimates of fixed effect (structural) parameters and their associated random effect parameters are listed in Table 3. No covariate (SAPS II score, gender, group, age, BW) showed any significant influence on the fitting. Individual Bayesian parameter estimates are displayed in Table 4.

Discussion

We have studied the potential effect of several covariates on the pharmacokinetics and on the pharmacodynamics of norepinephrine, in patients with severe trauma or septic shock, using mixed effect modelling with NONMEM. The main findings of the present study were: (1) norepinephrine kinetics were best described using a one-compartment linear model and norepinephrine clearance was negatively related to SAPS II score taken as a global indicator of illness severity, (2) MAP was related to norepinephrine plasma concentration but no covariate was able to describe the observed inter-individual variability.

Norepinephrine is metabolized by two major intracellular enzymes.[18] The redundancy in the metabolizing enzymes and transporters may explain why saturation kinetics are not seen even at the concentrations achieved by exogenous administration. It has been shown, in dogs, that exogenously administered norepinephrine was eliminated primarily by the liver.[19] Additional elimination also occurs in the kidney and capillary walls, especially in lungs. Norepinephrine clearance is, therefore, related to cardiac output.[20]

In our study, norepinephrine kinetics were best fitted using a linear one-compartment model with first order elimination. Johnston and colleagues[6] recently showed that norepinephrine pharmacokinetics are predictable in patients with head trauma. These authors found that norepinephrine plasma levels were correlated with norepinephrine infusion rates, without any significant influence on plasma clearance. These data were consistent with single-compartment, first-order kinetics for norepinephrine. The norepinephrine pharmacodynamics were however unpredictable. No correlation was found between norepinephrine plasma levels and

Table 4 Individual patient characteristics and Bayesian estimates of kinetic and dynamic parameters in the two groups. Group S, septic shock, T, trauma, PT, prothrombin time, CL, total body clearance, V, volume of distribution, $T_{1/2}$, terminal half-life, Clearance non-parametric, clearance measured as the ratio between the infusion rate and the concentration measured just before the first increase in dosing

Group	Gender	Weight (kg)	Age (yr)	Serum creatinine (μM)	PT (%)	SAPS II	Clearance (non-parametric) (ml min^{-1})	Clearance (NONMEM) (ml min^{-1})	V (ml)	MAP_0 (mm Hg)	MAP_{MAX} (mmHg)	EC_{50} (ng ml^{-1})	$T_{1/2}$ (min)
S	Male	66	68	181	77	19	2306	1810	9200	78.6	98.7	44.8	5.08
S	Male	78	56	298	100	20	9135	9140	6420	52.3	98.7	31.7	0.70
S	Male	65	55	76	79	25	9554	10 300	9700	67.8	98.7	31.5	0.94
S	Female	73.4	87	216	77	29	6683	4710	1130	67.8	98.7	174	0.24
S	Female	81	81	185	70	37	1756	2290	8530	67.3	98.7	75.3	3.72
S	Female	70	63	131	13	39	5907	6500	9220	64	98.7	169	1.42
S	Male	65	62	188	100	41	1742	1010	3840	85.5	98.7	33.2	3.80
S	Male	82	67	108	90	53	4931	4128	21 300	94.2	98.7	8.52	5.16
S	Female	48	80	167	68	56	216	288	6760	69.7	98.7	60.2	23.47
S	Female	65	72	105	41	56	914	871	8200	57.4	98.7	1078	9.41
S	Female	50	72	60	100	60	994	1070	7990	60.7	98.7	34	7.47
S	Male	60	53	231	45	66	88	69	2530	55.4	98.7	290	36.67
T	Male	89	27	73	100	20	4869	2760	6490	83	98.7	14.3	2.35
T	Female	60	20	71	49	24	3471	2400	9280	96.9	98.7	21.7	3.87
T	Male	65	35	69	96	25	1070	1300	13 700	62.2	98.7	28.2	10.54
T	Male	89	19	144	62	26	4524	5290	17 100	79.6	98.7	76	3.23
T	Female	75	64	60	75	27	4767	1330	8730	73.4	98.7	176	6.56
T	Male	70	34	89	98	30	1561	1190	3930	66.3	98.7	16.3	3.30
T	Female	67	28	50	82	33	3298	2760	8990	69.7	98.7	30.7	3.26
T	Male	83	37	287	34	33	2491	2680	4680	65	98.7	47.4	1.75
T	Male	55	44	54	98	35	2528	2570	8610	72.8	98.7	220	3.35
T	Female	55	22	114	68	37	1454	1240	8950	67.4	98.7	82.2	7.22
T	Female	68.5	23	71	76	41	192	271	4890	67.4	98.7	179	18.04

changes in MAP. In a study describing the pharmacokinetics of epinephrine and norepinephrine in patients following cardiac arrest, Prengel described two-compartment, linear kinetics for epinephrine.[21] In contrast, norepinephrine kinetics exhibited a single exponential decay. The single compartment kinetics occurred at concentrations similar to those measured in our study. In critically ill children, Fisher and colleagues[22] suggested linear pharmacokinetics for epinephrine. In the present study, even in patients with impaired metabolic function, saturation kinetics were not observed and the correlation between the two methods used for calculating clearance (non-parametric estimation and compartmental analysis) showed excellent agreement.

Ensinger and colleagues,[23] in healthy volunteers, showed a linear relationship between norepinephrine dosing and plasma concentrations. In head-injured patients, Johnston and co-workers described a linear relationship between norepinephrine infusion rate and plasma concentration.[6] These authors failed to demonstrate any clear relationship between norepinephrine infusion rate and clearance. We did not observe any relationship between norepinephrine dosing and concentrations because of major inter-individual variability both in volume and clearance. Thus, we have looked for covariates to explain this variability. Only the SAPS II score was significantly inversely correlated with clearance. The volume of distribution did not correlate with any of the potential covariates tested. The immediate consequence of this decreased body clearance with increased severity score was an increased terminal half-life in the most severely ill patients. Nevertheless, differences in SAPS II score could not exclusively explain the large variability in clearance. Indeed, with constant dose norepinephrine infusion, plasma concentration could exhibit only a 3-fold variation, depending on the patient's severity scaled on the SAPS II score. Therefore, the residual variability independent of the patient's SAPS II score remains to be explained.

Previous pharmacokinetic studies with catecholamines have found similar variability. With dopamine, in volunteers,[5] there was both intra- and inter-subject variability in infusion rate and resulting serum concentrations. MacGregor and colleagues[7] found that dopamine dose based on BW did not yield consistent, predictable plasma concentrations in a population of healthy male subjects. Interestingly, Johnston and co-workers,[6] reported a clear relation between dopamine infusion rate and clearance, thus suggesting either non-linear kinetics for dopamine or that increasing the dose increases the cardiac output and therefore total body clearance. Other studies have reported a wide variability with dobutamine[8] in critically ill surgical patients, making standard pharmacokinetic modelling of less utility than for other drugs, and that dopamine clearance is lower in critically ill patients and has a large interindividual variation.[24] We found that the only variable that significantly influenced norepinephrine clearance was the severity of illness.

The changes in mean arterial pressure adequately fitted an E_{max} model incorporating the individual kinetic parameters estimated at the first stage. The population estimate of EC_{50}, was 70 μg ml^{-1} with a wide inter-individual variability (the

95% CI, 62–420 $\mu g\ ml^{-1}$). The absence of a single covariate to explain this variability, is likely to be due to the small number of patients studied, leading to a lack of power of our study. Differing effects of the severity illness on pharmacokinetics and pharmacodynamics may explain these results. Indeed, the most severely ill patients had a lower clearance and needed less drug to achieve a predetermined concentration. However, we anticipated a shift to the right of the dose–effect curve in these patients with the most severe illness. This lack of relationship between infusion rate, plasma concentration, and haemodynamic parameters has been reported previously[6] for both dopamine and norepinephrine. Impaired vascular reactivity had been shown in trauma[9] and in septic shock[10] patients. In trauma, impaired pressor sensitivity to catecholamines has been demonstrated in animals.[25] MacArthur and colleagues[1] have previously shown that inactivation of catecholamines by superoxide anions contributes to the loss of vascular reactivity to norepinephrine and the subsequent hypotension that develops in Gram-negative endotoxic shock. Recent studies have related this vasopressor dependency to abnormal adrenocortical function observed in inflammatory consequences of septic[26] and hemorrhagic shock.[27] The intensity of this is considered proportional to the severity of the shock. Our study did not significantly relate any factors to this hyporeactivity. Indeed, in healthy volunteers, Ensinger and co-workers[23] also failed to show a relationship between norepinephrine concentration and haemodynamic variables.

In conclusion, an inverse relationship between norepinephrine clearance and severity illness was found. We failed to find any clear factor explaining the pharmacodynamic variability. This suggests the primary factor of variability in dose is pharmacokinetic.

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