ELIMINATION OF NADOLOL BY PATIENTS WITH RENAL IMPAIRMENT

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1 Nadolol excretion was studied in 24 patients with chronic renal failure.

2 The amount of nadolol excreted during the 120-h period after receiving the drug ranged from less than 1% in functionally anephric patients up to 11.5% in patients with average creatinine clearance of 57.9 ± 3.6 ml/min/1.73 m^2.

3 Renal clearance of nadolol was found to correlate with creatinine clearance; nadolol elimination is retarded in patients with renal failure.

4 Nadolol serum half-life is prolonged in proportion to the remaining renal function. Therefore, dosage intervals in renal patients receiving nadolol should be adjusted to creatinine clearance.

5 Haemodialysis effectively reduced serum concentration of the drug; it may therefore be a useful therapy for drug intoxication.

Introduction

PATIENTS with chronic renal failure frequently require a number of drugs during treatment. Many of these therapeutic agents are excreted, at least partially, by the kidney and tend to accumulate in blood (Beerman *et al.*, 1977; Craig & Rifkin, 1977; Lavene *et al.*, 1977), resulting in an increased incidence of adverse reactions or intoxications (Smith *et al.*, 1966). These complications (Dettli *et al.*, 1970) can be prevented or minimized by reducing the dose or prolonging the dose frequency.

β-adrenoceptor-blocking agents are a common therapy used in chronic renal patients with hypertension or coronary heart disease. Nadolol is a non-selective β-adrenoceptor-blocking agent, recently described by Lee *et al.* (1975, 1977). The drug has proved to be effective in the treatment of hypertension, angina pectoris and cardiac arrhythmias (Frithz, 1978; Furberg *et. al.*, 1978; Vukovich *et. al.*, 1976). Studies in normal volunteers and hypertensive patients have shown that maximum plasma concentrations of nadolol occur 3-4 h after oral dosing and that the terminal half-time for elimination usually ranges between 14-20 h and exhibits dose dependency (Vukovich *et al.*, 1976). About 60% of the absorbed nadolol is eliminated unaltered by the kidneys and a smaller fraction is eliminated by non-renal routes, probably by way of biliary excretion. Binding to plasma proteins is in the range 25-30% (Dreyfuss *et al.*, 1977).

The present study was designed to evaluate the excretion of nadolol by the kidney in patients with varying degrees of chronic renal failure and to determine the effectiveness of haemodialysis in removing the drug from the circulation.

Methods

Patient population

Twenty-four hypertensive patients (13 males, 11 females) with varying degrees of renal impairment participated in this study. The males ranged in age from 18-74 yr, the females from 22-71 yr. The patients were segregated into four groups of six, based on the degree of renal impairment. Mean corrected creatinine clearance of the four groups were 1.7 ± 0.3, 10.7 ± 2.3, 33.8 ± 3.7 and 57.9 ± 3.6 ml/min/1.73 m^2. Informed written consent to participate in the study was obtained from each patient before enrolment. This study received Institutional Review Committee approval.

Study protocol

Each patient received a single 80 mg oral dose of nadolol during hospitalization. Samples of blood (12 ml) were collected immediately before (0 h) and at 4, 8, 12, 24, 48, 72 and 96 h after ingestion of nadolol. Urine samples were collected as follows: a random sample was collected just before drug administration and the total volume of urine excreted

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for the 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 h periods was also collected. The sample collection schedule was followed for 72 h only in patients requiring a haemodialysis. Patients on chronic haemodialysis received a second 80 mg oral dose of nadolol approximately 2 weeks later, 4 h before dialysis. Dialysis was accomplished by means of a Drake–Willock artificial kidney and a Cordis–Dow hollow fibre dializer, with a single-pass flow of 120 litres of dialysate (Diasol, Travenol) for each 6-h dialysis. Blood flow through the dializer was adjusted for each patient and ranged from 150-200 ml/minute.

During dialysis, arterial and venous blood samples were collected from the blood lines. These were taken at the start of dialysis and 2, 4 and 6 h after dialysis was begun. Dialysate samples (30 ml) were collected at the beginning and 2, 4 and 6 h after the start of haemodialysis. Vital signs were measured frequently during the study and a battery of clinical laboratory tests were carried out before and after nadolol administration.

Nadolol assay

After clotting, blood samples were centrifuged, and the serum supernatant removed and stored at —10°C until assayed. Aliquots (15 ml) of each urine collection and the 30 ml dialysate samples were also stored at —10°C until assayed. Nadolol assays were carried out using a fluorometric method (Ivashkiv, 1977).

Results

Serum pharmacokinetics

Individual maximum serum concentrations as high as 440.3 ng/ml were observed after administration of nadolol. The range was 50.4-440.3 ng/ml. Graphs that correlated serum concentration with time were constructed for each patient. From the resultant curves, the terminal phase (β) slope was estimated and serum half-life determined. These data are summarized in Table 1. As can be seen, the serum half-life for nadolol was inversely proportional to creatinine clearance. Individual values varied from 18.2-68.6 hours. Mean values were as low as 26.1 ± 2.8 h in group IV and increased to 44.7 ± 6 h in group I.

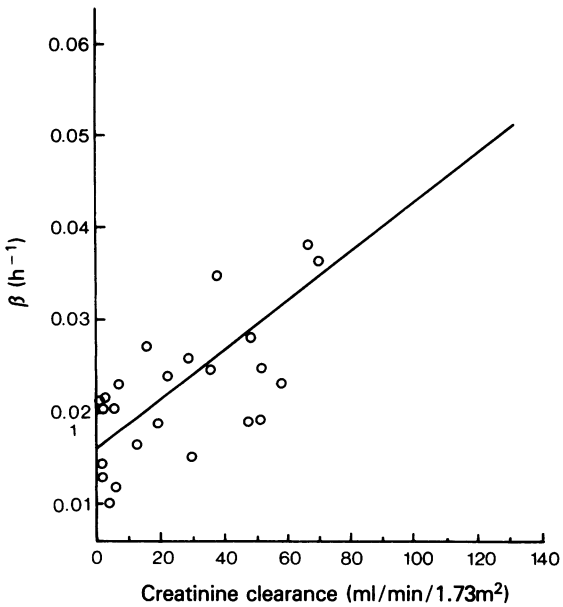

Figure 1 Relationship of terminal rate constant (β) to creatinine clearance. $\beta = 0.0163 + 0.000\,261\ Cl_{Cr}$; $r = 0.79$; $P < 0.001$.

The slope β was 0.01168 ± 0.002 in group I and increased in each group to a maximal value of 0.0282 ± 0.0031 in group IV. This relationship between creatinine clearance and the terminal slope β is shown in Figure 1. As can be seen, there is a linear correlation with a very significant correlation coefficient of 0.79 and a P value less than 0.001. The intercept of the equation describing this relationship, 0.0163, represents the excretion of nadolol by non-renal routes. It is interesting to point out that this value is similar to those obtained in patients of group I, who were practically anephric.

Table 1 Serum pharmacokinetic parameters for nadolol

Group no.	Corrected creatinine clearance ± s.e. (ml/min/1.73m²)	Slope (β) ± s.e.	Serum half-life (h) Range	Serum half-life (h) Mean ± s.e.
I	1.7 ± 0.3	0.0168 ± 0.0020	32.2-68.6	44.7 ± 6.0
II	10.7 ± 2.3	0.0195 ± 0.0022	29.7-58.2	38.6 ± 4.4
III	33.8 ± 3.7	0.0238 ± 0.0027	20.0-45.9	31.2 ± 3.7
IV	57.9 ± 3.6	0.0282 ± 0.0031	18.2-36.5	26.1 ± 2.8

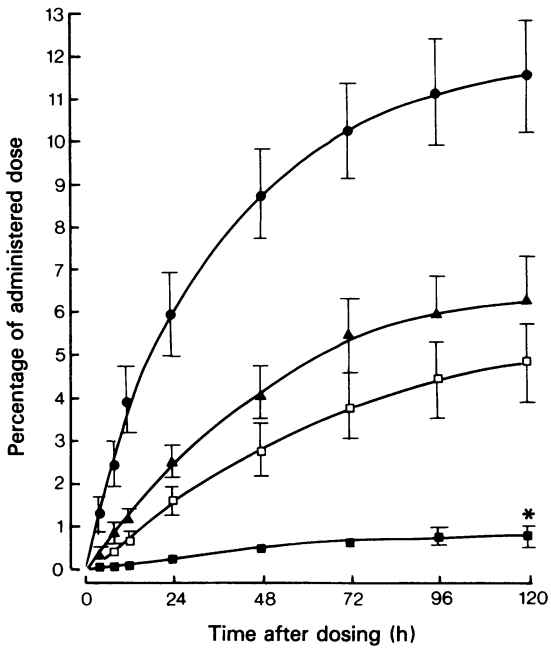

Figure 2 Average urinary excretion of nadolol by the four patients groups: ■, I (estimated); □, II; ▲, III; ●, IV. *Estimated

Urinary elimination

Table 2 shows the urinary elimination data for the four groups. The terminal slope β was 0.0194 ± 0.0027 in group I and increased to 0.0281 ± 0.002 in group IV. The excretory half-life of nadolol by individual patients ranged from 21-52.9 hours. Mean excretory half-lives ranged from 25.5 ± 2.2 h for group IV patients to 39.2 ± 5.1 h in group I patients.

Figure 2 shows the fraction of nadolol dose excreted by the patients during the 120-h period after drug administration. It was less than 1% in patients of group I and increased to approximately 11.5% in patients of group IV.

Renal clearance of nadolol was determined using the estimated serum concentrations at the midpoints of each urine collection period during the interval between 12 and 120 h after drug administration. This relationship is shown in Figure 3. The linear regression line can be described by the equation: $Cl_{nadolol} = 0.612\ Cl_{creatinine} + 1.76$. This plot has a correlation coefficient of 0.93 ($P < 0.001$).

Haemodialysis studies

Each of the patients in group I received a second 80 mg oral dose of nadolol approximately 2 weeks

Table 2 Urinary elimination of nadolol

Group No.	Corrected creatinine clearance ± s.e. (ml/min/1.73m²)	Slope (β) ± s.e.	Excretory half-life (h) Range	Excretory half-life (h) Mean ± s.e.	Mean nadolol excretion (mg) ± s.e. 0-72 h	Mean nadolol excretion (mg) ± s.e. 0-120 h
I	1.7±0.3	0.0194±0.0027*	23.8-52.9	39.2±5.1	0.50±0.11	0.63±0.11*
II	10.7±2.3	0.0229±0.0022	22.7-38.9	31.3±2.7	—	3.87±0.74
III	33.8±3.7	0.0238±0.0026	21.0-43.6	31.0±3.4	—	5.07±0.82
IV	57.9±3.6	0.0281±0.0020	21.7-35.4	25.5±2.2	—	9.23±1.02

*Estimated

Table 3 Nadolol serum concentrations during haemodialysis

Patient No.	Corrected creatinine clearance (ml/min/1.73m²)	Haemodialysis time (h) Pre A	Pre V	Pre Δ	2 A	2 V	2 Δ	4 A	4 V	4 Δ	6 A	6 V	6 Δ
2	1.4	110.0	112.3	2.3	157.0	103.1	53.9	116.8	95.0	21.8	106.2	81.2	25.0
4	1.8	509.8	495.5	14.3	297.8	232.3	65.5	267.4	178.7	88.7	235.1	172.9	62.2
12	1.5	117.3	114.4	2.9	81.5	64.4	17.1	75.6	52.0	23.6	93.4	71.4	22.0
14	3.1	180.7	170.7	10.0	597.5	480.7	116.8	483.1	416.4	66.7	340.4	236.6	103.8
16	1.2	245.6	261.1	15.5	176.1	107.5	68.6	154.4	124.8	29.6	108.6	83.4	25.2
17	0.9	—	—	—	76.9	52.3	24.6	61.9	39.7	22.2	66.6	51.2	15.4
Mean ± s.e.	A	232.7±32.9			231.1±80.3			193.2±65.3			158.4±43.5		
	V	230.8±32.0			173.4±66.8			151.1±56.9			116.1±29.6		
	Δ	1.9± 5.2			57.8±14.6			42.1±11.7			42.3±14.0		

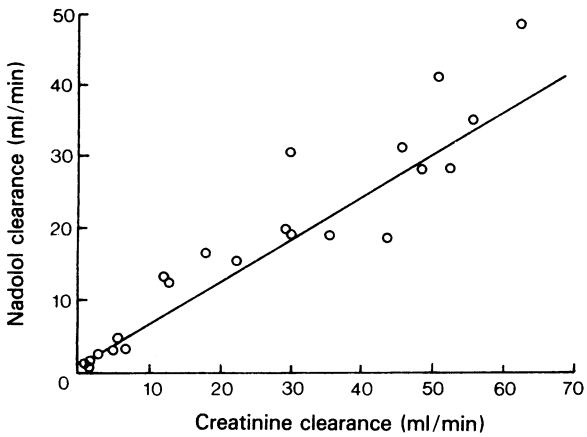

Figure 3 Urinary clearance of nadolol by patients with impaired renal function.

after the initial study. This second dose was administered 4 h before the start of haemodialysis when maximum serum concentrations would be expected. Individual arterial and venous nadolol serum concentrations estimated during haemodialysis are displayed in Table 3 and depicted graphically in Figure 4. Mean A-V differences at 2, 4 and 6 h were estimated to be 57.8 ± 14.6, 42.1 ± 11.7, and 42.3 ± 14.0 ng/ml, respectively. Expressed as a fraction of the arterial concentration, a quotient of about 0.25 is estimated. This fraction was reasonably consistent both throughout the dialysis periods and between patients. Table 4 shows the mean nadolol serum half-life in haemodialysis patients before and during haemodialysis. In every case the serum half-life decreased markedly. The mean value before dialysis was 39.2 ± 5.1 h and during haemodialysis it was 4.4 ± 0.9 hours.

The concentration of nadolol in the dialysate was measured at the same times as arterial and venous

Table 4 Nadolol serum half-lives before and during hemodialysis

Patient No.	*Corrected creatinine clearance (ml/min/1.73m²)*	*Serum half-life (h) Non-dialyzed*	*dialyzed*
2	1.4	42.5	8.5
4	1.8	23.8	3.0
12	1.5	36.5	5.1
14	3.1	52.9	3.1
16	1.2	26.9	3.3
17	0.9	52.5	3.6
Mean±s.e.	1.7±0.3	39.2±5.1	4.4±0.9

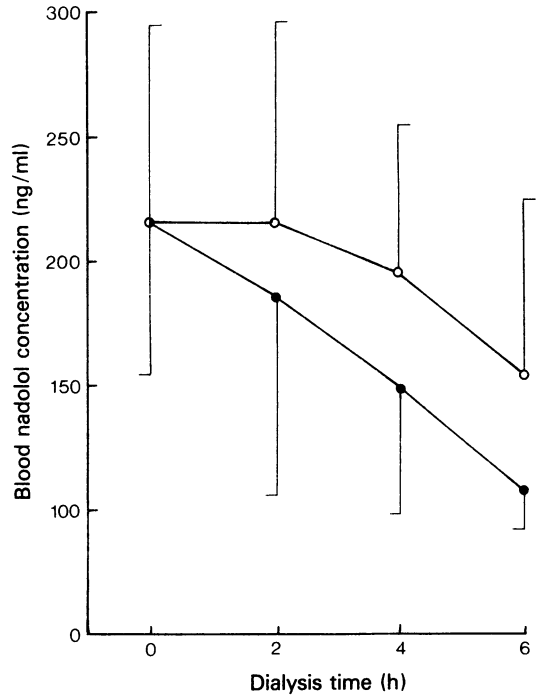

Figure 4 Mean arterial (○) and venous nadolol serum concentrations (●) during haemodialysis.

samples were obtained. Nadolol clearance by haemodialysis (dialysance) was calculated for each patient (Table 5). Clearance ranged from 17.7-176.2 ml/min at specific intervals during dialysis. Mean clearance values for individual patients ranged from 46.4-102.0 ml/minute.

Vital signs and laboratory test results

Except for the 12-h measurement, the average heart rate was significantly decreased between 2 and 96 h after nadolol ingestion. The average reduction was 16 beats/min at 4 hours. Mean BPs on average

Table 5 Nadolol dialysance (ml/min)

Patient No.	*Time after start of dialysis (h) 2*	*4*	*6*	*Mean*
2	48.4	53.9	66.4	56.2
4	75.4	54.0	17.7	49.0
12	67.5	64.8	84.0	72.1
14	57.7	37.6	43.9	46.4
16	71.0	58.0	44.2	57.7
17	176.2	92.9	36.8	102.0
Mean±s.e.	82.7±19.1	60.2±7.5	48.8±9.5	

remained below the control measurements for the full 12-h study period. Indeed, the average BPs measured between 24 and 120 h after the administration of nadolol were generally significantly less than the control values. Although this is not an unexpected consequence of β-adrenoceptor blockade, the relationship of this observation to bed rest conferred by hospitalization cannot be ruled out. One patient developed orthostatic hypotension during measurement of standing BP but suffered no sequelae. Follow-up evaluations made a week after completion of the study did not reveal any persistent changes in vital signs indicative of continued β-blockade. Except for a transient SGOT elevation in two patients, no clinical laboratory abnormalities could be attributed to nadolol. Side-effects reported by patients included bradycardia, malaise, dizziness associated with postural hypotension, and diarrhea. All reactions were self-limiting and the patients returned to their pre-study conditions at the conclusion of this investigation.

Conclusions

These results demonstrate that nadolol excretion is retarded in patients with renal failure. As occurs with a variety of other agents, the rate of excretion is determined by the remaining renal function. There was a direct correlation of nadolol excretion and creatinine clearance. The serum half-life of nadolol, which is unusually long in normal subjects (14-20 h) was prolonged up to 45 h in patients with severe renal damage. In order to avoid or minimize accumulation of nadolol, patients with renal failure should receive the drug at intervals according to their creatinine clearance, particularly when this is lower than 30-50 ml/minute. The data acquired from this study have enabled us to estimate the rate of elimination of nadolol by non-renal routes. The half-life for non-renal elimination is approximately 42.5 h, similar to the half-life observed in patients who are functionally anephric (group I). This calculated rate is also consistent with the observation of about 70% renal excretion observed after intravenous administration of nadolol in patients with normal renal function (Dreyfuss *et al.*, 1977).

The studies in patients on chronic haemodialysis demonstrate that nadolol can be efficiently extracted from the circulation by this procedure. In the six patients studied the venous concentration was approximately 25% lower than the arterial concentration; and the serum half-life during haemodialysis was 4 hours. The accessibility of nadolol to the dialysis medium is consistent with its low order of binding to plasma proteins (about 25-30%). Therefore, haemodialysis may be a useful therapy in situations of drug accumulation particularly in chronic renal patients in haemodialysis programs.

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