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DICLOFENAC, PARACETAMOL, AND VIDARABINE REMOVAL DURING PLASMA EXCHANGE IN POLYARTERITIS NODOSA PATIENTS

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ABSTRACT

Since plasma exchange (PE) represents a major treatment for patients suffering from systemic diseases, its influence on the kinetics of three drugs was investigated: vidarabine, used in patients with polyarteritis nodosa associated with hepatitis B virus (eight subjects), and diclofenac and paracetamol for investigative purposes (five subjects). This study confirmed that vidarabine is so rapidly deaminated to form hypoxanthine arabinoside (Hx-Ara) that no detectable concentrations were measured. Hx-Ara levels were used to evaluate vidarabine kinetics; $19{\cdot}5 \pm 14{\cdot}6$ mg of Hx-Ara were removed by one PE during the first week of treatment ($15\,mg\,kg^{-1}\,d^{-1}$, continuous infusion) and $7{\cdot}8 \pm 10{\cdot}2$ mg were eliminated by one PE during the second week of treatment ($7{\cdot}5\,mg\,kg^{-1}\,d^{-1}$, continuous infusion). Based on the vidarabine intake per hour and the resulting quantity of Hx-Ara removed per hour, PE recovery was quite important (ca. 30 per cent), during both the first and second weeks of continuous infusion. Data were subject to large interindividual variability. However, these results do not favor vidarabine dosage supplementation in this indication because the duration of PE is less than 8 per cent of a daily administration period. For paracetamol (1 g, single oral dose) and diclofenac (100 mg, single oral dose), the fractions of drug removed during PE effected within 2h of drug intake, were respectively $5{\cdot}0 \pm 3{\cdot}1$ per cent and $13{\cdot}6 \pm 9{\cdot}5$ per cent, while plasmapheretic clearance reached, respectively, $13{\cdot}0 \pm 10{\cdot}7$ per cent of the systemic clearance for paracetamol and $23{\cdot}0 \pm 1{\cdot}0$ per cent for diclofenac.

KEY WORDS Plasma exchange Pharmacokinetics Diclofenac Paracetamol Vidarabine Polyarteritis nodosa

INTRODUCTION

Plasma exchange is now classically used for the treatment of systemic vasculitis, such as polyarteritis nodosa (PN), because it effectively removes circulating immune complexes.

However, obviously, with plasma exchange (PE), endogenous and xenobiotic

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components can also be removed and a few studies have described PE application to cases of drug overdose.[1–7] For that reason, we decided to study, in patients with histologically demonstrated PN, the influence of PE on the pharmacokinetics of vidarabine, a drug of major interest when PN is associated with hepatitis B virus (HBV).[8,9] The second purpose of this study was to investigate possible changes in the kinetic parameters of diclofenac and paracetamol during PE, in patients with PN not associated with HBV. Protein binding and volume of distribution (V_d) are two relevant parameters for plasma exchange, since they provide predictive values of PE effectiveness[10–13] as classically described. The diametrically opposed values exhibited by diclofenac[14] (plasma protein binding >99 per cent; $V_d = 0{\cdot}1$ l kg^{-1}) and paracetamol[15] (plasma protein binding <5 per cent; $V_d = 1{\cdot}1$ l kg^{-1}) explains the interest in their inclusion.

METHODS

Patients

Thirteen patients (Table 1) with histologically confirmed PN participated in the study. Eight of them (group 1) were infected with HBV and they were treated by continuous infusion of vidarabine for 3 weeks, during which time 15 PE were performed. The other five patients (group 2) received diclofenac and paracetamol (during and outside the PE period).

Informed consent was obtained from each patient before entry into the study, which had been approved by the Local Scientific Committee for Human Subject Investigations.

Plasma exchange

PE were performed using the Dideco Vicacell system. The plasma volume of each subject was based on body weight (bw) and one hematocrit measured before PE. Each PE removed 60 ml of plasma kg^{-1} bw. To restore the circulating mass, a replacement solution consisting of 4 per cent albumin and 500 ml of gelatin was infused throughout each PE procedure, which removed 2200–4900 ml of plasma within 3 h.

Administration procedure

Group 1: vidarabine dissolved in 5 per cent dextrose was continuously infused for 3 weeks as follows: 15 mg kg^{-1} d^{-1} for the first week, then 7·5 mg kg^{-1} d^{-1} for the next 2 weeks. *Group 2*: after an 8 h fast, and 1 to 2 h before PE, patients ingested orally 100 mg of diclofenac (Voltarene® tablet) and 1 g of paracetamol (Doliprane® tablet) with 100 ml of water. One week later, the

Table 1. Characteristics of the study populations

Subject number	Age (y)	Sex	Weight (kg)	Serum creatinine ($\mu mol\,l^{-1}$)	Albumin ($g\,l^{-1}$) first exchange	Albumin ($g\,l^{-1}$) last exchange
Group 1 PN + HBV:vidarabine						
1	63	F	45	50	37	32
2	52	F	58	44	34	30
3	48	M	52	62	38	36
4	59	M	66	69	36	40
5	76	M	63·5	90	40	39
6	55	M	43	64	39	38
7	65	F	45	65	36	31
8	30	M	58	260	39	39
Group 2 PN:diclofenac-paracetamol						
9	81	F	55	120	38	37
10	64	F	75	66	43	40
11	57	M	57	227	36	–
12	56	M	69	120	34	35
13	61	M	69	68	30	34

PN:periarteritis nodosa; HBV:hepatitis B virus.

same medications were readministered to the patients to study diclofenac and paracetamol pharmacokinetics without PE.

Blood sampling

Group 1: blood samples were taken from the forearm opposite to that of the infusion site and were drawn into heparinized tubes containing ca. 50 μg of adenosine deaminase inhibitor (Pentostatin, Warner Lambert Company, Ann Arbor, MI)[16,17] to prevent *in vitro* deamination. The collection schedule was one sample 10 to 30 min before PE, then every 15 min during PE and 1, 2, 3, 4, and 5 h after PE. For each patient, blood sampling took place on the fourth day of the first and of the second week and, for the study of vidarabine kinetic parameters without PE, blood samples were collected every 30 min for 2 h then every hour for 5 h as soon as the last $7{\cdot}5\,mg\,kg^{-1}\,d^{-1}$ infusion was stopped. *Group 2:* blood samples were collected just prior to the ingestion of diclofenac and paracetamol, then 1 h and 0·5 h before PE; then they were drawn every 15 min during PE and 1 and 2 h after PE. For the study without PE, blood was collected at time zero and 0·5, 1, 1·5, 2, 3, 4, and 5 h post-ingestion of medication. In all cases, samples were immediately centrifuged, aliquoted in duplicate and stored at −20°C until analysis. An aliquot of total PE volume was also taken and frozen until quantitation.

Drug analysis

These three drugs were evaluated using high pressure liquid chromatography (HPLC) methods. Assays described by Ameer *et al.*[18] and Said and Sharaf[19] were used, respectively, for paracetamol and diclofenac measurements. The linear regression constants for each drug are given in Table 2. The limits of

Table 2. Regression analysis of the calibration curves of paracetamol, diclofenac, vidarabine, and Hx-Ara

Drug	Drug concentration $mg\,l^{-1}$	Equation*	r^2	n†
Paracetamol	1–20	$y = 4{\cdot}2x + 0{\cdot}4$	0·996	6
Diclofenac	0·1–5	$y = 0{\cdot}24x + 0{\cdot}015$	0·997	6
Vidarabine	0·1–10	$y = 0{\cdot}71x + 0{\cdot}09$	0·998	7
Hx-Ara	0·1–10	$y = 0{\cdot}6x + 0{\cdot}01$	0·999	6
	10–40	$y = 1{\cdot}05x + 0{\cdot}4$	0·996	5

* x = Drug concentration, y = relative peak height ratio of drug to internal standard.
† Number of points on the curve.

detection were $1\,mg\,l^{-1}$ of paracetamol and $0{\cdot}1\,mg\,l^{-1}$ of diclofenac, using 1 ml plasma samples. Average recovery ranged from 92·6 to 95·7 per cent for paracetamol and 89·5 to 93·1 per cent for diclofenac. The coefficient of variation (CV per cent) for paracetamol and diclofenac, respectively, ranged from 1·1 to 8·7 per cent and 1·3 to 6·7 per cent for within-day determinations, and from 1·1 to 10·3 per cent and 1·4 to 10·1 per cent for day to day determinations. Vidarabine and Hx-Ara were monitored with UV detection as described by Bowman and Kauffman[17] with minor modifications to obtain better sensitivity. Three milliliters of acetone were added to 1 ml of a plasma sample, containing paracetamol (100 µl of a 10 mg/ml water solution) as an internal standard. The tube was vortexed for 30 s and centrifuged for 15 min at 2000**g**. The supernatant was separated and evaporated to dryness under a stream of air. The dried sample was reconstituted with 1 ml of dichloromethane and 0·5 ml of 1·25 mM sodium heptane sulfonate (pH 8). After gentle mixing and a second centrifugation, 20 µl of the aqueous supernatant were injected into the chromatograph. The detection wavelength was 259 nm. For both vidarabine and its metabolite hypoxanthine arabinoside (Hx-Ara) detection limits were 0·1 mg/l. The linear regression constants are given in Table 2. Recovery of vidarabine from plasma concentrations of 0·5, 1, and 5 mg/l was 78, 80, and 84 percent, respectively. Recovery of Hx-Ara from plasma concentrations of 2·5, 10, and 40 mg/l was 75, 82, and 86 per cent, respectively. The coefficients of variation for vidarabine and Hx-Ara, respectively, ranged from 4·0 to 13·7 per cent, and 3·2 to 9·6 per cent for within-day determinations and from 5 to 16 per cent and 4 to 10·6 per cent for day to day determinations.

Pharmacokinetic calculations: without PE

Estimation of the apparent rate constant for elimination (β) and half-life ($t_{1/2\beta}$) were obtained from least squares line analysis of the semi-logarithmic plot of plasma concentrations versus time. The area under curve (AUC) was calculated by application of the trapezoidal rule to the area up to the end of the sampling period. The AUC was extrapolated to infinity (AUC_∞) by adding the latter concentration measured divided by β. Systemic clearance (Cl_T/F) was calculated by dividing the dose by AUC_∞, where F is the bioavailability factor. The apparent volume of distribution ($V_{d\beta}/F$) was expressed as Cl_T/F divided by β.

During PE

The total amount of the drug, Q_{PE}, removed during PE can be defined as follows: $Q_{PE} = C_{PE} \times V_{PE}$ where C_{PE} is the concentration of drug measured after shaking V_{PE}, the total filtered volume of PE. Thus, the fraction of drug removed can be obtained from the ratio Q_{PE}/TBS, where TBS is the total body store of the drug prior to the onset of PE. TBS can be calculated as the product of $V_{d\beta}$ and the concentration of drug just before PE (C_{SE}).

Clearance during plasmapheresis (Cl_{PE}) can be evaluated as the ratio Q_{PE}/AUC_{PE}, where AUC_{PE} represents the area under the curve during PE. To calculate the area under the curve during PE, one can take either the plasma drug concentration at the midpoint time of PE[11] (method 1): $AUC_{PE} = T \times C_{pmid}$, where T is the duration of PE, or concentrations just before and just after each procedure[20] (method 2): $AUC_{PE} = T \times [(C_{SE} + C_{end}/2]$, or the integral of the plasma drug concentration versus time curve during PE (method 3).

Statistical analysis

Results are given as means $\pm$SD unless stated otherwise. The non-parametric Friedman test was used to compare Cl_{PE} obtained using three methods of calculating AUC_{PE}, and the predetermined level of significance was $p < 0{\cdot}05$.

RESULTS

Group 1

Despite a low detection limit and the presence of an *in vitro* inhibitor, vidarabine itself could not be detected. As in other reports,[16,21,22] Hx-Ara (plasma protein binding < 5 per cent;[23] $V_d = 0{\cdot}61\,kg^{-1}$)[24] levels were used to describe the pharmacokinetics of the parenteral compound during PE as long as no concentration of vidarabine could be detected. Strong evidence indicates that deamination of vidarabine is immediate and total. PE efficacy is shown in

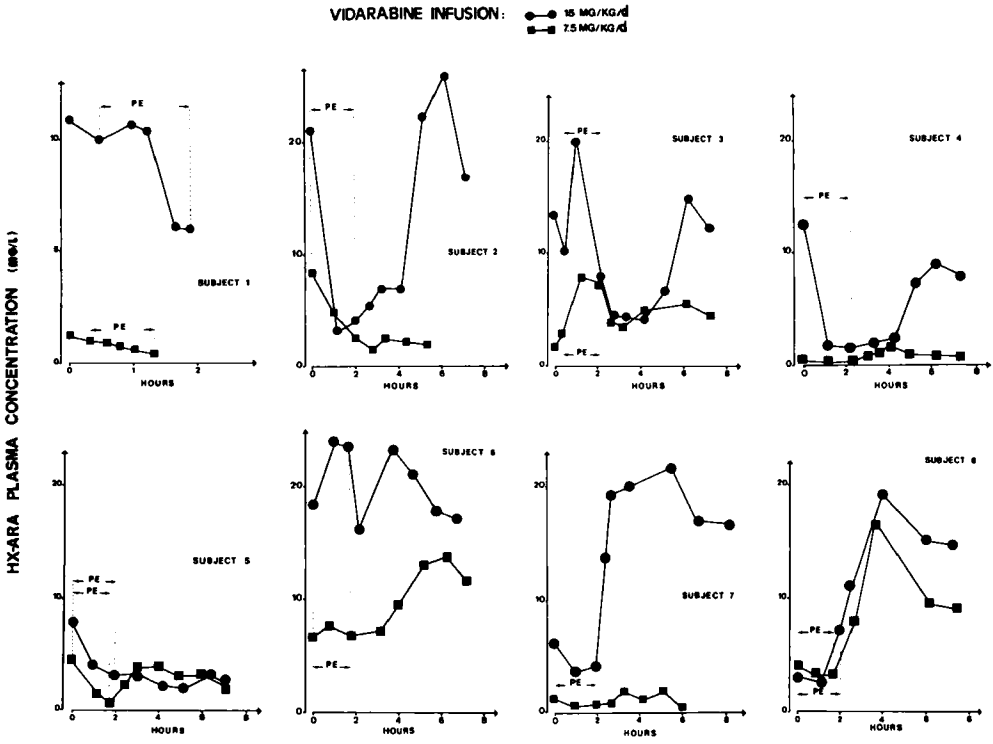

Figure 1. Plasma levels of hypoxanthine arabinoside (Hx-Ara) during the continuous infusion of 15 mg kg^{-1} d^{-1} (●) and 7·5 mg kg^{-1} d^{-1} (■) of vidarabine in eight patients. PE (period of plasma exchange)

Figure 1 for each of the eight patients. Once PE has been terminated, a rebound in the plasma concentration occurs possibly due to a redistribution of drug from the tissue to the vascular compartment. Total amounts of Hx-Ara removed during PE, Q_{PE}, were respectively, 19·5 ± 14·6 mg (range: 6 to 28·6 mg; 1st week PE, 15 mg kg^{-1} d^{-1}) and 7·8 ± 10·2 mg (range: 0·5 to 25 mg ; 2nd week PE, 7·5 mg kg^{-1} d^{-1}). Clearance during PE, Cl_{PE}, at the same times reached, respectively, 34·2 ± 37·3 ml min^{-1} (range: 5·0 to 119 ml min^{-1}; 15 mg kg^{-1} d^{-1}) and 22·7 ± 16·8 ml min^{-1} (range: 6·1 to 55 ml min^{-1}; 7·5 mg kg^{-1} d^{-1}).

Tables 3 and 4 present individual data concerning PE efficacy for the two dosages, expressed as the ratio of Q_{PE} (Hx-Ara) per hour to vidarabine intake per hour; 31 and 26 per cent of the total Hx-Ara concentration were lost, respectively, during the first week (15 mg kg^{-1} d^{-1}) and second week (7·5 mg kg^{-1} d^{-1}) PE. Indeed, the average PE duration (1·75 h) represents less than 8 per cent of a daily continuous administration of vidarabine which is surely negligible, despite the loss of 30 per cent of the drug administered during PE.

Table 3. PE efficacy observed after 4 days of continous infusion of vidarabine ($15\,mg\,kg^{-1}\,d^{-1}$) in eight patients

Patients	Vidarabine intake (a) ($mg\,h^{-1}$)	PE length (h)	Q_{PE} Hx-Ara (b) ($mg\,h^{-1}$)	PE recovery Ratio b/a
1	28·1	1·75	6·0	0·21
2	36·2	2·0	5·1	0·14
3	32·5	1·67	3·6	0·11
4	41·2	1·5	5·8	0·14
5	39·7	1·92	5·6	0·14
6	26·9	1·75	16·0	0·59
7	28·1	1·5	13·2	0·47
8	36·2	2·0	24·5	0·67
Mean	33·6	1·75	10·0	0·31
SD	5·5	0·20	7·3	0·23
CV (%)	16·4	11·4	73·0	74·2

CV: coefficient of variation = (SD/mean) 100.

Table 4. PE efficacy observed on the fourth day of the second week of continous infusion of vidarabine ($7{\cdot}5\,mg\,kg^{-1}\,d^{-1}$) in eight patients

Patients	Vidarabine intake (a) ($mg\,h^{-1}$)	PE length (h)	Q_{PE} Hx-Ara (b) ($mg\,h^{-1}$)	PE recovery Ratio b/a
1	14·0	1·0	1·5	0·11
2	18·1	2·0	2·6	0·14
3	16·2	1·8	0·3	0·02
4	20·6	2·3	0·3	0·01
5	19·8	1·9	2·8	0·14
6	13·4	1·75	13·2	0·98
7	14·0	1·5	0·4	0·03
8	18·1	1·67	11·4	0·63
Mean	16·8	1·74	4·1	0·26
SD	2·8	0·38	5·2	0·35
CV (%)	16·6	21·8	126·8	134·6

CV: coefficient of variation = (SD/mean) 100.

Group 2

The main kinetic parameters of paracetamol and diclofenac and the PE efficacy for each molecule are given in Table 5. The kinetic constants observed in this study without PE, on a small sample size ($n=5$) are, however, quite similar to those found in the literature.[15] The drug concentration versus time profiles during and without PE for paracetamol and diclofenac are presented in Figures 2 and 3, respectively. The rebound in plasma concentrations, observed with paracetamol, in subjects 9, 10 and 12, likely due to the redistribution of the drug from the tissues, is worth noting while nothing similar is

reflected by the kinetic parameters of diclofenac (small $V_{d\beta}$, high protein binding). The fraction of the drug removed from the body by PE (Q_{PE}/TBS) reached 5·0 ± 3·1 per cent for paracetamol and 13·6 ± 9·5 per cent for diclofenac. Therefore, these results were in accord with the different pharmacokinetics of these agents.

Table 5. Pharmacokinetic parameters without PE, and PE efficacy evaluated following a single oral dose of paracetamol (1 g) and diclofenac (100 mg) ($n = 5$)

	Paracetamol			Diclofenac		
	Mean	SD	Range	Mean	SD	Range
Without PE						
Cl_T/F (ml min^{-1})	317	134	(125–475)	120	53	(63·5–177)
$V_{d\beta}$ (l kg^{-1})	1·00	0·08	(0·9–1·10)	0·20	0·03	(0·15–0·25)
During PE						
Q_{PE} (mg)	27	6·8	(17–33)	1·8	1·3	(0·5–3·8)
TBS (mg)	612	205	(324·5–882)	19·8	15·2	(9·8–46·2)
Q_{PE}/TBS (%)	5·0	3·1	(2·5–10)	13·6	13·6	(1·1–22·0)
$CL_{PE}/(CL_T/F)$ (%)	13	10·7	(6·3–32)	23·0	31·0	(8·0–80·0)

PE clearance

Table 6 presents the Cl_{PE} values obtained using three different modes of calculating AUC_{PE}. In our study, 5–8 blood samples were collected during each PE, and experimental AUC_{PE} was calculated using the trapezoidal rule (method 3). For paracetamol the three methods are equivalent. For diclofenac, although no statistical difference was found, it is worth noting the great variation in the plasma concentrations in subjects 9, 10, and 11 whose PE kinetic curves (Figure 3) hardly resemble a monoexponential decline. For vidarabine, the calculations using method 2 led systematically to lower but not significantly different results. Although these differences are not statistically significant, the best method giving a good estimation of clearance is that based on the AUC of plasma concentrations during the PE session. It must be emphasized that the precise determination of the AUC of plasma concentrations requires numerous blood samples during a time span as short as a PE session (an average of 1·75 h).

DISCUSSION

As we had thought, indeed it was our initial hypothesis, the volume of distribution and the extent of binding to plasma proteins are the essential factors in the extraction of medications by PE. The results obtained with paracetamol,

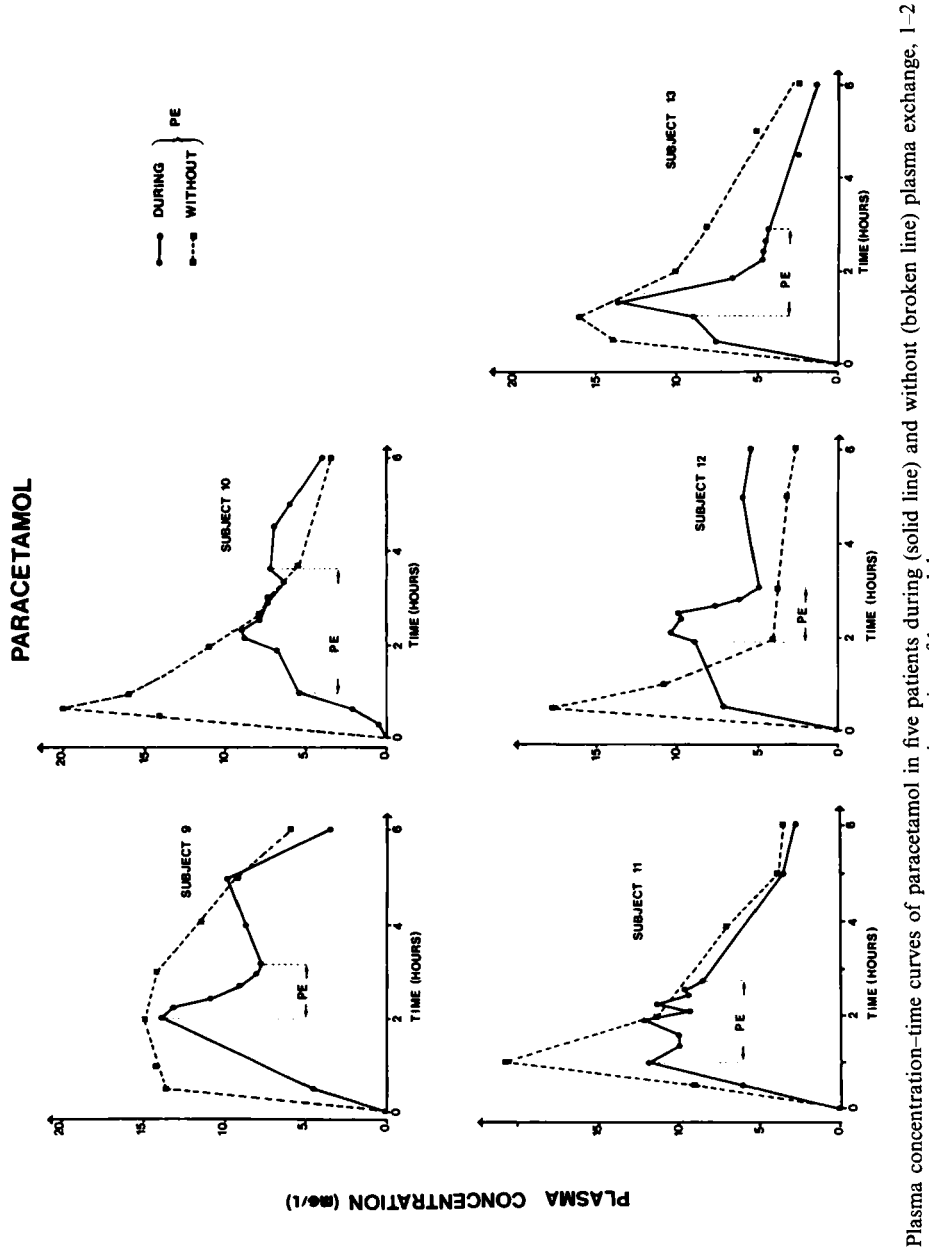

Figure 2. Plasma concentration–time curves of paracetamol in five patients during (solid line) and without (broken line) plasma exchange, 1–2 h after ingestion of 1 g oral dose

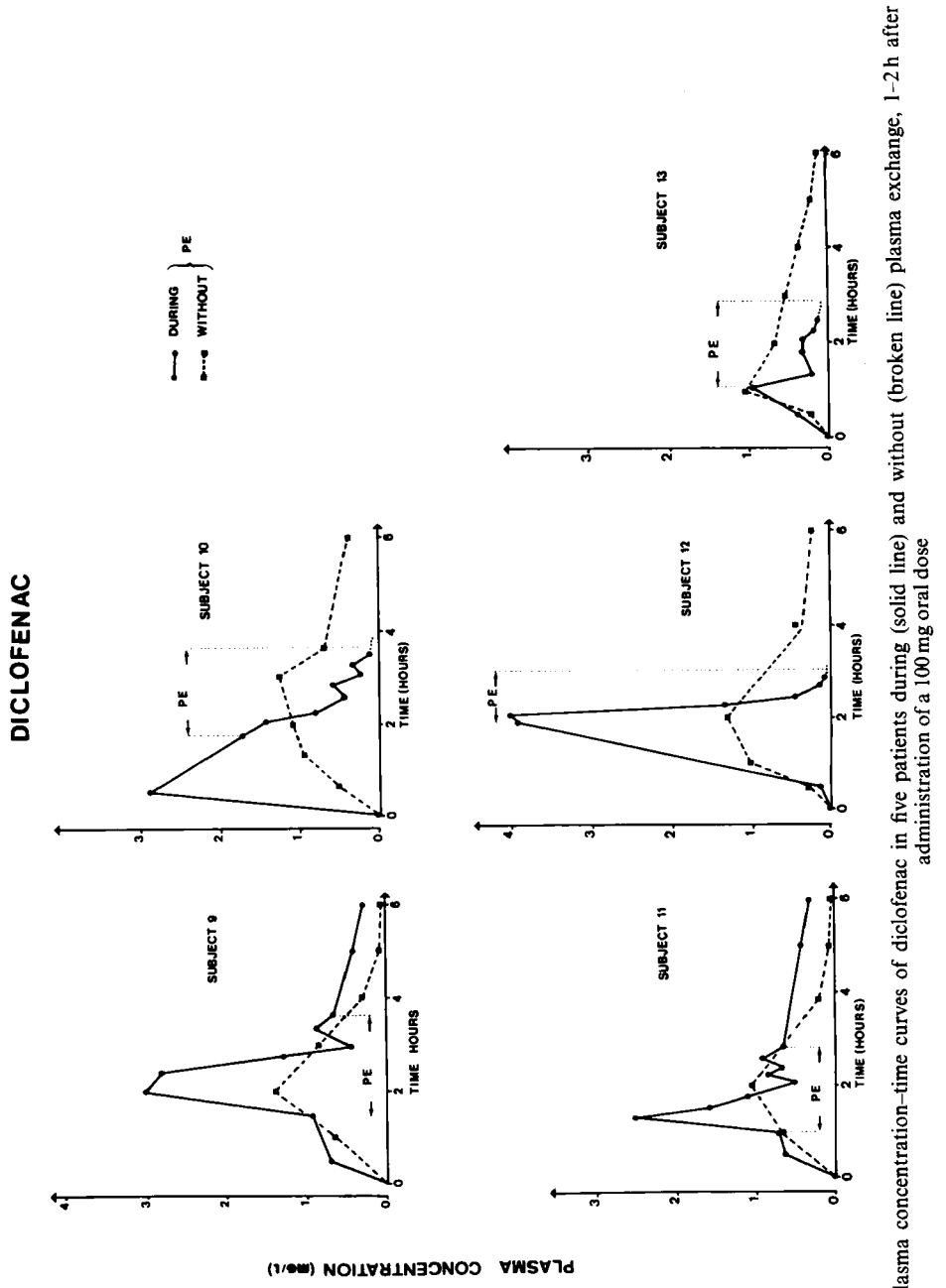

Figure 3. Plasma concentration–time curves of diclofenac in five patients during (solid line) and without (broken line) plasma exchange, 1–2 h after administration of a 100 mg oral dose

Table 6. Cl_{PE} (Q_{PE}/AUC_{PE}): comparison of values obtained using three methods for calculating AUC_{PE}

Method	Paracetamol (1 g)	Diclofenac (100 mg)	Vidarabine $7.5\,mg\,kg^{-1}\,d^{-1}$	Vidarabine $15\,mg\,kg^{-1}\,d^{-1}$
1	28·5 ± 8·6	33·8 ± 31·8	31·4 ± 25·2	39·3 ± 37·7
2	31·5 ± 7·2	20·3 ± 11·8	19·2 ± 14·6	29·2 ± 41·1
3	31·1 ± 5·3	19·3 ± 18·5	22·7 ± 16·8	34·2 ± 37·4

Statistical analyses were not significant.
See methods for the formulas used to calculate AUC_{PE}.

diclofenac, and vidarabine confirm this hypothesis. Thus we can propose, as Gwilt and Perrier[25] did for hemodialysis, an index predictive of drug extraction by PE: $\Phi = 7{\cdot}5\,(1 + f_u)/V_d$ where f_u is the fraction which is not bound to plasma proteins and V_d is the volume of distribution. This index represents the fraction of drug in extracelluar fluids.[26] Figure 4 shows the relationship between the fraction of dose eliminated, f_e, during a PE session, and this index for a given number of drugs. The fraction eliminated during PE is approximately the seventh of the fraction of drug in extracellular fluids. For an index < 20, extraction is weak ; the amount extracted only becomes significant for an index > 50.

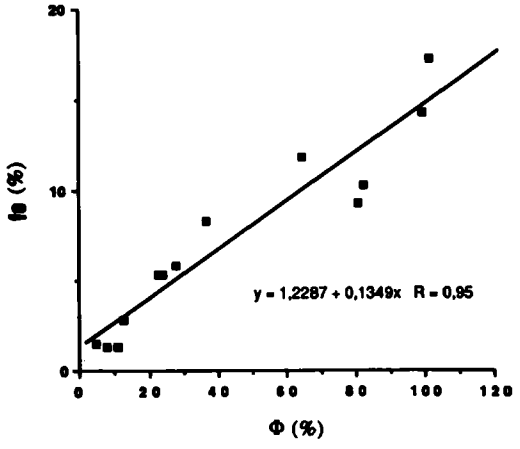

Figure 4. Relationship between the fraction of the drug eliminated during a PE session (f_e) and the fraction of the drug in extracellular fluids (Φ) (from previously reported results[3,4,7,11,12,13,20])

Drug extraction by PE can be evaluated in different ways : amount eliminated, fraction purified or PE clearance ; each approach has its own advantages and disadvantages which must be addressed. The best parameter for quantifying drug extraction and evaluating the effectiveness of PE is the determination of the fraction purified which, in practice, is not always possible because it is necessary to know the $V_{d\beta}$ (TBS = $V_{d\beta} \times C_{SE}$). PE clearance does not predict

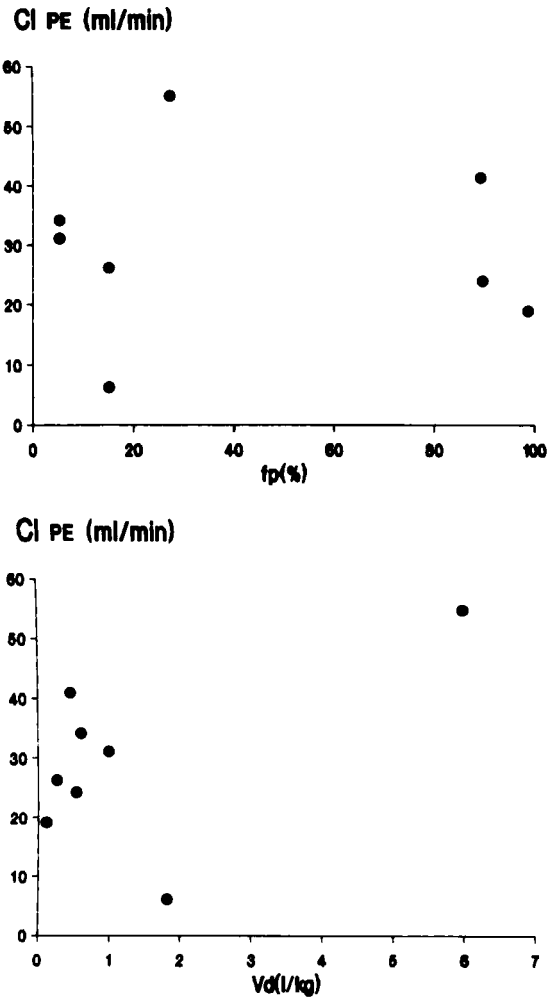

Figure 5. Relationship between the PE clearance and the level of binding of plasma proteins (f_p) (top) and the volume of distribution (V_d) (bottom) (from previously reported results[3,4,7,11,12,13,20])

the extent of extraction and cannot be correlated to the V_d or the fraction bound to plasma proteins. Indeed, Figure 5 shows the lack of correlation between clearance and V_d or the fraction bound to plasma proteins (f_p).

From our results, it follows that the lower the V_d and the higher the f_p, i.e. the greater the fraction of the dose administered which is present in the vascular compartment, the greater the elimination by PE, and, in turn, effectiveness of PE.

Thus, consequences of alteration of plasma protein binding on elimination during PE, can be predicted. Hypoalbuminemia (25 $g l^{-1}$) leads to a reduced

elimination half-life, increased volume of distribution, and decreased plasma concentrations.[20] This results in a lower extraction of the drug during PE. In our patients, the albumin concentrations at the first and the last PE were similar (Table 1), within the normal range, and therefore did not affect the other parameters.

Practically speaking, other than for medications with low V_d and strong binding to plasma proteins, it does not seem necessary to envisage changes in the doses administered. In contrast, for drugs with a low V_d and a low therapeutic index, a heavy dose pre-exchange or a replacement post-exchange must be anticipated. For perfused drugs, it is possible to increase the flow to compensate for the clearance due to PE.

To conclude, it must be remembered that the patients investigated here were suffering from diseases with extensive vascular complications leading to hemodynamic disorders. This has to be taken into account when medication is given (especially orally) in association with PE. For example, one patient with polyarteritis nodosa suffered acute bowel ischemia, thus explaining, *a posteriori*, why diclofenac levels were detected only 5 h after drug intake and long after PE; hence, this patient had to be excluded from the study because oral administration was clinically ineffective until PE had been terminated. In this complex disease, many factors preclude a more precise assessment of the effect of PE on drug pharmacokinetics. Since estimates of pharmacokinetic parameters are subject to great inter- and intra-subject variabilities, depending upon the physiological status of the individual, a better evaluation of PE requires (1) cross-over studies (with and without PE); (2) starting the PE procedure at a time when the theoretical distribution phase of the drug has been reached; (3) evaluation of the decline of plasma concentrations over a period after PE which is long enough to permit the assessment of all the redistribution obtained between intra- and extra-vascular compartments.

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