J. Pharm. Pharmacol. 1991, 43: 371–374
Communicated November 26, 1990

Plasma volumes, blood volumes, and plasma protein concentrations after moderate haemodilution with Fluosol-DA or normal saline in the rat

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Abstract—Plasma volumes, blood volumes, and plasma total protein, albumin, and bilirubin concentrations have been determined in rats for 72 h following 20 or 40 mL kg^{-1} haemodilution with Fluosol-DA or 0·9% NaCl. Haemodilution with 20 mL kg^{-1} of either haemodiluent had no influence on the measured values. Plasma and blood volumes did not change after Fluosol-DA haemodilution at 40 mL kg^{-1}, but albumin and bilirubin concentrations were decreased for 72 h. Only bilirubin concentrations were decreased for 72 h following haemodilution with 40 mL kg^{-1} of 0·9% NaCl. It was concluded that changes in a drug's plasma protein binding, and not the plasma or blood volume, are responsible for the reported alterations in a drug's apparent volume of distribution after haemodilution.

Investigations in rats have shown that the apparent volume of distribution (Vd) of several drugs changes in a time-dependent (Shrewsbury 1986; Shrewsbury et al 1987a, b; Shrewsbury & White 1989a, 1990a; Hoke 1989) and haemodilution volume-dependent (Hodges et al 1983, 1984; Matsumoto-Kikuchi et al 1983; Kemner et al 1984; Shrewsbury et al 1989; Shrewsbury & White 1990b) manner after haemodilution with Fluosol-DA (Fluosol) or other blood substitutes. In each of those reports, a monoexponential equation was fitted to the plasma or blood concentration vs time data, and the Vd was calculated as the dose divided by the theoretical concentration at time zero (i.e. C_0). Two physiological responses to haemodilution could change C_0: (1) a change in plasma or blood volume; (2) a change in drug binding to plasma proteins. The purpose of this investigation was to determine if plasma and blood volumes were significantly altered for 72 h after haemodilution with Fluosol or 0·9% NaCl (saline). Saline haemodilution was included in the study to differentiate the effects of Fluosol and haemodilution alone.

Materials and methods

Materials. Fluosol was donated by Alpha Therapeutic Corp. (Los Angeles) and prepared as directed within 0·5 h of use. Indocyanine green (ICG) (Sigma Chemical Co.) was dissolved in Sterile Water for Injection USP (5 mg mL^{-1}) 5 min before use. Only one ICG lot was used to avoid variation in the impurity content (Heintz et al 1986). Male Sprague-Dawley, rats were used with free access to food and water. Animal weights in the 20 mL kg^{-1} segment of the study averaged 302 ± 41 g and 356 ± 34 g in the 40 mL kg^{-1} part of the study.

Methods. A recent report has shown that the circulating blood volume can be accurately measured using an ICG dilution method (Busse et al 1990). Animals were cannulated and haemodiluted as previously described with 20 or 40 mL kg^{-1} of Fluosol or saline (Shrewsbury 1986). ICG was intravenously administered (5 mg kg^{-1}) through the cannula 0·5, 24, 48 and 72 h after haemodilution. Blood samples (0·2 mL) were collected at 1, 1·5, 2, 3, and 4 min after dosing, and analysed the same day by a spectrophotometric method (Shrewsbury et al 1987b). A monoexponential equation was fitted to the ICG blood concentration vs time data (NLIN/SAS) and the ICG Vd was calculated from the final estimate of C_0. The blood volume was determined as Vd/0·915 to correct the large vessel haematocrit to the whole body haematocrit (Albert 1971; Busse et al 1990). Plasma volumes were calculated from the determined blood volume and the measured haematocrit using the equation:

$$\text{plasma volume} = \text{blood volume}(1-0{\cdot}87*\text{Hct}/100)$$

where Hct is the measured haematocrit, and 0·87 is the product of (0·915)(0·96); 0·96 is the estimated correction for the percent of plasma entrapped in the haematocrit cells (Albert 1971; Guyton 1991). Averaged data were assessed by the Wilcoxon rank sum test (SAS) with a probability of $P < 0{\cdot}05$ considered statistically significant.

One blood sample was collected 3 h after ICG administration through the cannula and the plasma harvested. The plasma sample was analysed the same day for total plasma protein (total protein), plasma albumin (albumin), and total plasma bilirubin (bilirubin) concentrations with analytical kits (Sigma Chemical Co.). The standard curves were prepared using plasma from unexchanged rats, or rats which had been haemodiluted with the appropriate haemodiluent for the appropriate time interval.

Results

The results are shown in Tables 1 and 2. The control values for total protein, albumin, blood volume, and plasma volume are less than reported normal values (Mitruka & Rawnsley 1977). The total protein and albumin concentrations were expected to be less than normal since animals had been cannulated, dosed and sampled, and allowed to recover for 3 h. The blood volume and plasma volume are approximately 55 and 70% of reported normal values, respectively. The blood volume normalized for body weight was approximately 3%, compared with the reported normal value of 5–7% (Mitruka & Rawnsley 1977; Hebden et al 1990). The blood volume may have been reduced as an acute (24 h) consequence of cannulation. Blood volume tended to increase in unexchanged animals that remained cannulated for 72 h; however, none of these preliminary values were statistically different from control values (data not shown).

Blood and plasma volumes were not statistically different from control volumes after 20 or 40 mL kg^{-1} haemodilution with either haemodiluent. Haemodilution with 20 mL kg^{-1} had no influence on total protein, albumin, or bilirubin concentrations. However, haemodilution with 40 mL kg^{-1} of Fluosol significantly reduced albumin concentrations throughout the 72 h study. Haemodilution with 40 mL kg^{-1} of saline did not decrease albumin concentrations. Bilirubin concentrations were less than control values in every group following 40 mL kg^{-1} haemodilution.

Discussion

The aim of this investigation was to determine if changes in the Vd of several drugs after haemodilution could be explained in terms of an altered plasma or blood volume. Haemodilution would necessarily reduce plasma protein concentrations. Investigations in severely haemodiluted rats (haematocrit = 2–3%) have shown that total protein and albumin were reduced following haemodilution, and that significant recovery of these

Table 1. Averaged blood volumes, plasma volumes, and plasma constitutents after haemodilution with 20 mL kg^{-1} of Fluosol or saline (n = 4–6).

	Treatment groups								
		Fluosol				Saline			
	Control	0·5 h	24 h	48 h	72 h	0·5 h	24 h	48 h	72 h
Blood volume (mL kg^{-1})	32·7 (19·7)	35·4 (18·6)	42·1 (19·9)	22·1 (9·4)	46·9 (17·2)	41·5 (10·5)	34·1 (19·1)	33·0 (6·0)	36·3 (10·8)
Plasma volume (mL kg^{-1})	23·4 (15·8)	26·8 (14·1)	34·7 (17·8)	16·0 (7·1)	36·6 (13·4)	31·1 (7·9)	26·2 (14·3)	27·0† (3·7)	27·7 (7·8)
Total protein (g dL^{-1})	3·4 (1·2)	3·7 (0·3)	3·2 (0·6)	3·5 (0·2)	3·6 (0·3)	3·1† (0·2)	4·3 (0·9)	3·9 (1·0)	3·4 (1·1)
Albumin (g dL^{-1})	2·1 (0·2)	2·2 (0·2)	1·9 (0·1)	2·1 (0·1)	2·1 (0·1)	2·2 (0·1)	2·4† (0·2)	2·0 (0·3)	1·9 (0·6)
Bilirubin (mg dL^{-1})	0·35 (0·14)	0·22 (0·07)	0·28 (0·13)	0·29 (0·09)	N.D.	0·33 (0·23)	0·30 (0·08)	0·22 (0·15)	0·33 (0·22)

Values are means (±s.d.) ($P < 0·05$). †Significantly different from corresponding Fluosol group. N.D. not determined.

Table 2. Averaged blood volumes, plasma volumes, and plasma constitutents after haemodilution with 40 mL kg^{-1} of Fluosol or saline (n = 4–6).

	Treatment groups								
		Fluosol				Saline			
	Control	0·5 h	24 h	48 h	72 h	0·5 h	24 h	48 h	72 h
Blood volume (mL kg^{-1})	29·7 (14·3)	42·7 (17·0)	16·7 (7·4)	42·7 (23·6)	23·2 (5·0)	24·1† (11·1)	34·7† (7·3)	33·0 (18·2)	19·0 (6·3)
Plasa volume (mL kg^{-1})	19·6 (10·6)	33·4 (11·8)	13·1 (5·7)	34·3 (20·4)	17·9 (3·5)	19·4† (10·6)	29·2† (6·5)	27·0 (14·6)	14·5 (5·0)
Total protein (g dL^{-1})	4·5 (0·7)	3·1* (0·6)	3·7 (0·7)	4·7 (0·8)	4·9 (0·4)	4·3† (0·5)	4·6 (0·3)	4·4 (0·5)	5·6*† (0·2)
Albumin (g dL^{-1})	2·2 (0·3)	1·4* (0·2)	1·5* (0·2)	1·5* (0·2)	1·5* (0·1)	1·7† (0·1)	2·0† (0·3)	2·0† (0·3)	2·1† (0·6)
Bilirubin (mg dL^{-1})	0·35 (0·17)	0·14* (0·08)	0·07* (0·06)	0·06* (0·04)	0·03* (0·01)	0·10* (0·06)	0·05* (0·03)	0·14 (0·21)	0·02*† (0·01)

Values are means (±s.d.). *Significantly different from corresponding control ($P \leq 0·05$). †Significantly different from corresponding Fluosol group.

levels occurred within 24 h (Lowe et al 1982, 1985; Hardy et al 1983; McCoy et al 1985, 1989). Other studies have suggested additional mechanisms that could alter plasma or blood volume. Fournier et al (1980) reported that vascular concentrations of perfluorotributylamine (Fluosol 43) increased over 3 h after severe haemodilution. The simultaneously determined [^{131}I]-albumin volume showed that the increased Fluosol 43 concentrations resulted from water transfer from the vascular to interstitial fluid. Guidet et al (1987) suggested that vascular membrane permeability was altered after hypervolaemic haemodilution with albumin plus gelatin or gelatin alone. Klubes et al (1987) reported that the tissue-to-blood partition coefficient of [^{14}C]-iodoantipyrine was increased in Fluosol exchanged animals.

The results of this study indicate that plasma volume, blood volume, and total protein concentrations did not change after Fluosol or saline haemodilution even though changes in plasma protein concentrations, oncotic pressure, vascular water, membrane permeability, and/or tissue-to-blood partitioning presumably occurred. Changes in albumin and bilirubin concentrations occurred after 40 mL kg^{-1} Fluosol haemodilution, and these changes are most likely responsible for the observed alterations in the Vd of drugs (Gibaldi & McNamara 1978). In studies with 20 mL kg^{-1} of haemodilution, Vd values were seldom altered (Hodges et al 1983, 1984; Shrewsbury et al 1989; Shrewsbury & White 1990b). But in studies that used 40 mL kg^{-1} or more, Vd changes often occurred (Matsumoto-Kikuchi et al 1983; Kemner et al 1984; Shrewsbury et al 1989; Shrewsbury & White 1990b).

Many in-vitro reports of plasma protein binding interactions between Fluosol and drugs have been published (Parsons 1986, 1987; Graben & Parsons 1988; Parsons & Shih 1989; Punwani & Ravis 1989; Shah 1990). However, the overall in-vivo effect would be complex and perhaps not predictable as a reduced albumin concentration would decrease the number of albumin binding sites, but the reduced bilirubin concentration could free binding sites on the remaining albumin molecules. In fact, such a complex situation may be present in this investigation. ICG is extensively bound to albumin (Paumgarter 1975). After haemodilutions with Fluosol, a decreased number of albumin binding sites could increase ICG Vd, and overestimations of the plasma and blood volumes would result. Likewise, an increased number of binding sites could decrease ICG Vd, and the plasma and blood volumes would be underestimated. Another factor may further add to the complexity of the in-vivo effect. ICG was suspected of binding to Fluosol (Bizot & Rink 1985); thus, the ICG Vd could be decreased due to this haemodiluent binding,

and the plasma and blood volumes underestimated. However, in this study, the plasma and blood volumes after saline haemodilution would not be influenced by ICG binding to the haemodiluent, since ICG does not bind to saline. There were some statistical differences in the plasma and blood volumes between corresponding Fluosol and saline haemodilution groups, but these parameters were not consistently less in the Fluosol haemodilution groups compared with the saline haemodilution groups, showing that ICG binding to Fluosol had little influence on the in-vivo effect.

It was noted that 40 mL kg^{-1} haemodilution with saline did not reduce the albumin concentration but consistently decreased the bilirubin concentration. One possible explanation for this result is that Fluosol may interact with the analytical kits giving a depressed albumin concentration. Such an interaction has been reported between Fluosol and an analytical kit for heparin (Shrewsbury & White 1989b). Although this possible interaction was not specifically investigated in this study, all standard curves were prepared using blank plasma from unexchanged animals or animals haemodiluted with the appropriate haemodiluent. A more likely explanation is that saline haemodilution elicits a totally different haematological response from Fluosol haemodilution. In studies that included saline haemodilution, the pattern of change in the drug's Vd was different from the pattern of change in Vd after Fluosol haemodilution (Shrewsbury 1986; Shrewsbury et al 1987a, b, 1989; Shrewsbury & White 1990a).

The author gratefully acknowledges the technical assistance of Sharon R. Oliver and Lisa G. White, and funding by the National Heart, Lung, and Blood Institute (HL33227).

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J. Pharm. Pharmacol. 1991, 43: 374–376
Communicated December 11, 1990

Prediction of drug loss from PVC infusion bags

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Abstract—PVC: water partition coefficients for a series of 13 drugs have been calculated from literature data and a high degree of correlation with octanol: water partition coefficients demonstrated. The resulting model, log $P_{PVC} = -0.35 + 0.69$ log P, ($r^2 = 0.88$) has been prospectively tested with 10 drugs. All the test drugs were within the 95% confidence intervals associated with predicted log P_{PVC} values consistent with a valid model. In practice, predicted log P_{PVC} values may be used to estimate drug loss from the aqueous phase of PVC bags at equilibrium. Equations are described which enable calculation of likely drug loss from 100, 500 and 1000 mL PVC bags. It is recommended that this approach is used to identify drugs which are unlikely to be significantly absorbed into PVC.

The loss of some drugs from aqueous solutions stored in PVC bags has been well documented (Moorhatch & Chiou 1974; Cossum & Roberts 1981; Kowaluk et al 1981; Illum et al 1983; Nation et al 1983). Illum et al (1983) suggests that octanol: water partition coefficients can be used to predict sorption behaviour. In this study a predictive model is developed to estimate the sorption of any drug into PVC bags from literature data.

Materials and methods

Chemicals. The following drugs were used in the study: clonazepam (Roche, Switzerland), diclofenac (Ciba Geigy, Switzerland), flunitrazepam (Roche), fluphenazine (Squibb, USA), medazepam (Roche), naproxen (Sigma), nitrazepam (Roche), oxazepam (Wyeth & Brother, UK), phenobarbitone and promethazine (May & Baker, UK) and verapamil (Sigma).

Partition coefficients. Apparent octanol: water partition coefficient (P_{APP}) values were obtained from the literature (Tables 1, 2). Where necessary these were converted to the partition coefficient value for the un-ionized species using the equation described by Hansch (1973).

The partition coefficients between the PVC and aqueous phases, P_{PVC}, were obtained from the literature (Roberts et al 1980; Illum & Bundgaard 1982; Illum et al 1983). P_{PVC} values for clonazepam, medazepam, nitrazepam and oxazepam were calculated from literature data (Kowaluk et al 1981; Nation et al 1983) following measurement of pH at their respective equilibrium concentrations.

Measurement of partition coefficients. Drug loss from PVC bags was determined as described by Kowaluk et al (1981). The optical absorbance of samples (concentration < 30 mg L^{-1}) withdrawn at appropriate times was measured at the wavelength of maximum absorbance (Unicam SP1700 spectrometer) until equilibrium was reached. The drug loss for promethazine was remeasured at a pH value (pH = 6·00) intermediate to those in the original study by Kowaluk et al (1981), since the calculated P_{PVC} values differed by more than 1 order of magnitude.

The P_{PVC} value was calculated from:

$$P_{PVC} = \frac{(A_{std} - A_{aq})}{A_{aq}} \times \frac{V_{aq}}{V_{PVC}} \quad (1)$$

where A_{std} and A_{aq} are the absorbances of the aqueous standard and the aqueous solution in the PVC bag at equilibrium and V_{aq} and V_{PVC} are the respective volumes of the aqueous and PVC phases. Values for absorbance were between 0·10 and 0·90. V_{PVC} and V_{aq} were determined from the difference in weight between a full and dried bag converted into units of volume using the densities of PVC and saline, 1·244 g mL^{-1} (personal communication, Travenol Laboratories, Auckland, New Zealand) and 1 g mL^{-1}, respectively.

At equilibrium the pH of the solution was measured and the calculated P_{PVC} value corrected to obtain the un-ionised partition coefficient using the equation from Hansch (1973).

Modelling. A linear regression model was developed using BMDP (Department Biomathematics, UCLA, Los Angeles) from logarithms of P and P_{PVC} values in the literature (Cossum & Roberts 1981; Illum et al 1983; Nation et al 1983) (Table 1). The model was prospectively tested with the P_{PVC} values measured in this study and literature values from Roberts et al (1980) and Illum & Bundgaard (1982) (Table 2).

The 95% confidence intervals (CI) were calculated for predicted Log P_{PVC} values (Snedecor & Cochran 1967).

$$95\%\ CI = \pm 1.01 \sqrt{\frac{1.04 + (\log P - 3.98)^2}{87.46}} \quad (2)$$

Results and discussion

The equation of best fit was:

$$\log P_{PVC} = -0.35 + 0.69 \log P \quad (3)$$

with the intercept significantly different from 0 and the slope significantly different from 1 ($P < 0.01$). A good fit resulted, with a correlation coefficient (r^2) of 0·88 (n = 25).

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