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The Effect of Moderate Haemodilution with Fluosol-DA or Hespan on the Nonmicrosomal Acetylation of Sulphadimidine in the Rat

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Abstract—The effects of Fluosol-DA (Fluosol) and Hespan haemodilution on the nonmicrosomal acetylation of sulphadimidine were studied in male rats. Fluosol increased the acetylsulphadimidine percent excreted in urine, the metabolic formation rate constant (k_f), and the formation clearance (CL_F) for 72 h after haemodilution without any significant changes in the sulphadimidine apparent volume of distribution (V_d) or total body clearance (CL). Hespan haemodilution increased the acetylsulphadimidine percent excreted in urine only at 48 h while significantly decreasing the sulphadimidine clearance, urinary excretion rate constant (k_u), and renal clearance (CL_R) for 72 h. The enhanced *N*-acetyltransferase activity after Fluosol haemodilution may have therapeutic consequences for concomitantly given drugs metabolized by this enzyme.

The importance of artificial blood substitutes has been underscored by the problems associated with the use of natural blood products, including disease transmission (e.g. AIDS, hepatitis) and donor-recipient incompatibility. Perfluorochemical (PFC) emulsions are capable of dissolving large volumes of oxygen and are being investigated as potential blood substitutes. One proprietary product (Fluosol-DA) has undergone extensive pre-clinical and clinical evaluation. It has been established that Fluosol-DA (Fluosol) and specifically the PFCs in the emulsion induce the phenobarbitone-inducible microsomal cytochrome P450 isoenzymes both in concentration and activity (Armstrong & Lowe 1989; Mishin et al 1989; Shrewsbury & White 1990a). Fluosol haemodilution decreased the nonmicrosomal sulphation of paracetamol at 48 h in rats (Shrewsbury & White 1990b).

The effects of Fluosol and Hespan haemodilution on nonmicrosomal sulphadimidine acetylation (Zidek & Janku 1979, 1981) in male rats are given in this report. The male rat was chosen as a model species since sulphadimidine acetylation displays a monomorphic distribution in-vivo (Zidek & Janku 1976; Tannen & Weber 1979; Weber & Hein 1985), which simplifies the interpretation of results. Also, changes in acetylation activity in male rats are manifested totally by changes in acetylsulphadimidine excreted in urine (Zidek & Janku 1981). The Hespan group was included in the study to differentiate the effects of the haemodilution mechanics from the effects of Fluosol itself. However, it is recognized that Hespan haemodilution may have its own unique effects.

Materials and Methods

Materials

Fluosol was donated by Alpha Therapeutic Corporation (Los Angeles, CA) and was prepared 0·5 h before use. Sulphadimidine was obtained from Sigma Chemical Co. (St Louis, MO), acetylsulphadimidine from ICN Biomedicals, Inc. (Costa Mesa, CA), and Hespan (6% hetastarch in 0·9% NaCl) from DuPont Pharmaceuticals (Wilmington, DE). HPLC grade solvents and buffers were obtained from commercial sources and used without further purification. Male Sprague-Dawley rats, 310–414 g, were used with free access to food and water.

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Methods

Animals were cannulated and haemodiluted as previously described (Shrewsbury et al 1987a) with 40 mL kg^{-1} of Fluosol or Hespan. The haemodiluted rats were compared with control rats which were cannulated but not haemodiluted. Sulphadimidine (10 mg kg^{-1}) was intravenously administered through the cannula 24, 48, or 72 h after haemodilution. Animals were placed in metabolic cages and urine was collected for 24 h.

Blood samples (0·3 mL) were taken at 2, 3, 5, 7, 9, and 12 h, and the plasma was immediately harvested, and stored at −20°C until assayed. Plasma sulphadimidine concentrations were determined by an HPLC procedure rather than a Bratton-Marshall based assay which underestimates the acetylated metabolite concentration (Whelpton et al 1981; Weber & Hein 1985). To 0·1 mL of plasma, 0·2 mL methanol and 0·04 mL internal standard (sulphathiazole 49·7 mg L^{-1} in water) were added. Samples were mixed, centrifuged for 2 min at 12 000 *g*, and 0·02–0·055 mL of supernatant injected. Chromatographic separation of sulphadimidine, acetylsulphadimidine, and the internal standard was achieved with a C_{18}, 10 μm Alltech column (4·6 × 250 mm), a mobile phase of 11:89 acetonitrile: 0·005 M sodium acetate (pH 5·7), and a flow rate of 2·0 mL min^{-1}. Ultraviolet absorbence was monitored at 254 nm (0·005 aufs) and sulphadimidine determined by peak area ratio. Standard curves for plasma sulphadimidine were linear from 2 to 50 mg L^{-1}. The standard curves were prepared using plasma from control animals or animals which had been haemodiluted with the appropriate haemodiluent.

At the end of the urine collection period, the pH was

measured (Alkacid pH kit, Fisher Scientific, Raleigh, NC), and the voided volume determined. Urine flow was calculated as voided volume per hour over the 24 h period. Urine samples were analysed by the HPLC assay described above. The urine samples were prepared by adding 0·03 mL water, 0·2 mL methanol, and 0·04 mL internal standard to 0·07 mL of urine. The samples were mixed, centrifuged for 2 min at 12000 *g*, and 0·020–0·045 mL of supernatant was injected. Standard curves for urine drug and metabolite were linear from 2 to 15 mg L^{-1}. The standard curves were prepared using urine from control animals or animals which had been haemodiluted with the appropriate haemodiluent. Preliminary experiments with urine samples treated with three different glucuronidase/sulphatase preparations confirmed that neither sulphadimidine nor acetylsulphadimidine was excreted as a glucuronide or sulphate metabolite.

The fitting of a monoexponential equation to the plasma concentration-time data was performed with the non-linear regression program NLIN of the Statistical Analysis System. The plasma concentration data were weighted by their squared reciprocals since the coefficient of variation was independent of the concentration assayed. The percent of drug or metabolite excreted in urine was calculated on a molar basis. The metabolite ratio was calculated as reported by Zidek & Janku (1976, 1979, 1981) as amount of metabolite excreted divided by the sum of amounts of drug and metabolite excreted. The sulphadimidine urinary excretion rate constant (k_u) was calculated as percent excretion times the overall elimination rate constant (k_{el}), and the metabolite formation rate constant (k_f) was calculated as percent metabolite excretion times k_{el}. Sulphadimidine renal clearance (CL_R) was calculated as percent excretion times total body clearance (CL). Metabolite formation clearance (CL_F) was calculated as percent metabolite excretion times CL. All values were corrected for the salt form and water of hydration.

Since acetylation of sulphadimidine has been reported to be normally distributed in male Sprague-Dawley rats (Dubbels et al 1980), Student's *t*-test was used in all two-group statistical comparisons assuming an equal variance within each group; a probability of $P \leq 0.05$ was considered statistically significant.

Results

Sulphadimidine plasma concentrations were adequately described with a monoexponential equation as expected (Dubbels et al 1980). Table 1 shows the averaged disposition parameters. The disposition parameters in the three control groups were constant indicating that cannulation for up to 96 h did not alter sulphadimidine pharmacokinetics. The apparent volume of distribution (V_d) was not reduced by either Fluosol or Hespan haemodilution. CL was only reduced at 48 and 72 h after Hespan haemodilution compared with the corresponding control groups. Half-life ($t_{\frac{1}{2}}$), dependent on both V_d and CL, reflected the changes in CL since V_d was unaltered.

Table 2 summarizes the urinary excretion data. Comparisons of the three control groups showed that the 72 h sulphadimidine excretion was decreased compared with the 24 h value, but not compared with the 48 h value; in the other groups, significant increases were seen at 24 h. For Fluosol, the metabolite excretion and metabolite ratio showed significant increases at all times studied. For Hespan, only the 48 h

Table 1. Averaged disposition parameters of sulphadimidine after haemodilution with 40 mL kg^{-1} of Fluosol or Hespan (n = 5–6).

	Treatment groups								
	24 h			48 h			72 h		
	Control	Hespan	Fluosol	Control	Hespan	Fluosol	Control	Hespan	Fluosol
$t_{\frac{1}{2}}$ (min)	208 (42)	270 (54)	260 (30)	210 (31)	326* (40)	268*† (37)	195 (31)	249* (32)	264* (24)
V_d (mL kg^{-1})	189 (22)	190 (18)	165 (23)	166 (22)	166 (20)	186 (21)	219 (68)	154 (24)	208 (67)
CL (mL min^{-1} kg^{-1})	0·65 (0·11)	0·51 (0·14)	0·45* (0·10)	0·56 (0·10)	0·36* (0·09)	0·48† (0·04)	0·80 (0·30)	0·44* (0·10)	0·54 (0·15)

Mean (s.d.). * Significantly different from corresponding control ($P \leq 0.05$). † Significantly different from corresponding Hespan ($P \leq 0.05$).

Table 2. Averaged urinary excretion percentages of sulphadimidine and acetylsulphadimidine after haemodilution with 40 mL kg^{-1} of Fluosol or Hespan.

	Treatment groups								
	24 h			48 h			72 h		
%	Control	Hespan	Fluosol	Control	Hespan	Fluosol	Control	Hespan	Fluosol
Sulphadimidine	11·6 (1·7)	9·1* (0·7)	16·4*† (3·4)	11·2 (3·3)	11·2 (2·0)	9·2 (3·0)	7·9‡ (0·8)	10·0 (2·3)	10·0 (2·3)
Acetylsulphadimidine	10·2 (3·8)	10·9 (3·5)	56·1*† (18·8)	8·5 (1·9)	14·5* (3·9)	25·6*† (5·4)	8·7 (6·1)	12·6 (5·0)	17·2* (5·9)
Metabolite ratio	49·1 (10·8)	57·0 (6·1)	79·3*† (3·1)	46·9 (7·3)	59·1* (8·9)	76·5*† (3·3)	52·2 (10·9)	58·1 (4·2)	65·4*† (5·7)

Mean (s.d.). * Significantly different from corresponding control ($P \leq 0.05$). † Significantly different from corresponding Hespan ($P \leq 0.05$). ‡ Significantly different from control at 24 h ($P \leq 0.05$).

Table 3. Averaged urinary excretion rate constant (k_u) and renal clearance (CL_R) of sulphadimidine and formation rate constant (k_f) and formation clearance (CL_F) of acetylsulphadimidine after haemodilution with 40 mL kg^{-1} of Fluosol or Hespan.

	Treatment groups								
	24 h			48 h			72 h		
	Control	Hespan	Fluosol	Control	Hespan	Fluosol	Control	Hespan	Fluosol
k_u ($min^{-1} \times 10^{-4}$)	4·0 (0·9)	2·4* (0·3)	4·4† (0·8)	3·7 (0·9)	2·4* (0·7)	2·4* (0·9)	2·8‡ (0·4)	2·8 (0·5)	2·7 (0·7)
CL_R (mL min^{-1} kg^{-1})	0·076 (0·020)	0·046* (0·009)	0·071† (0·012)	0·061 (0·014)	0·041* (0·017)	0·044 (0·013)	0·063 (0·024)	0·042 (0·008)	0·053 (0·013)
k_f ($min^{-1} \times 10^{-4}$)	3·3 (0·7)	2·8 (0·5)	14·9*† (4·1)	2·8 (0·6)	3·0 (0·5)	6·7*† (1·7)	3·0 (1·6)	3·5 (1·1)	4·5 (1·5)
CL_F (mL min^{-1} kg^{-1})	0·062 (0·009)	0·052 (0·008)	0·240*† (0·043)	0·047‡ (0·010)	0·050 (0·008)	0·123*† (0·020)	0·072 (0·063)	0·052 (0·013)	0·087 (0·020)

Mean (s.d.). * Significantly different from corresponding control ($P \leq 0·05$). † Significantly different from corresponding Hespan ($P \leq 0·05$). ‡ Significantly different from control at 24 h ($P \leq 0·05$).

group showed an increase in the metabolite parameters. The statistical conclusions were the same for calculations on a molar basis (data not shown).

Additional urinary and metabolic pharmacokinetic parameters are reported in Table 3. Sulphadimidine k_u was significantly reduced in the 72 h control group compared with 24 h; acetylsulphadimidine CL_F was reduced in the 48 h control group compared with 24 h. Fluosol haemodilution had little influence on k_u or CL_R, while Hespan haemodilution reduced both parameters at 48 h. These disposition changes were not due to gross changes in renal function as measured by urine volume, flow, or pH (see Table 4). Acetylsulphadimidine k_f and CL_F were significantly increased at 24 and 48 h, but not at 72 h, after Fluosol haemodilution. These increases mirrored the changes in the urinary metabolite parameters (Table 2). The changes in k_u and k_f were expected to follow those of CL_R and CL_F, respectively, since V_d was unchanged.

Discussion

The data in this report are consistent with literature reports on the pharmacokinetics and metabolism of sulphadimidine in the rat (Zidek & Janku 1976, 1979, 1981; Zidek et al 1977; Dubbels et al 1980; Vree & Hekster 1985).

The observed increases of acetylsulphadimidine excretion and CL_F indicate that Fluosol haemodilution resulted in a stimulation of drug acetylation in-vivo. The lack of change (or decrease) in CL would indicate that Fluosol increased acetylation at the expense of other metabolic pathways. This is evident by comparing the percentage of CL attributed to CL_R plus CL_F in control groups (approx. 20% in all three groups) with Fluosol haemodilution groups (69, 35 and 17 at 24, 48 and 72 h, respectively). Hespan haemodilution did not exhibit the magnitude nor the longevity of enhanced acetylation activity.

The elimination of sulphadimidine includes renal excretion of unchanged drug, acetylation, and other pathways. In a mass balance study with [^{14}C]sulphadimidine, 67·8 and 24·8% of the administered radioactivity was recovered in urine and faeces in 24 h (Paulson et al 1983). In the current report, only 20% of the dose was excreted as unchanged drug and the acetyl metabolite; thus, the other pathways account for as much as 40–50% of sulphadimidine disposition. Several other metabolites have been reported in rats (Olsen & Morland 1981; Paulson et al 1983; Paulson 1986). These reports followed metabolite concentrations for only 6 h or were in-vitro cell culture metabolism studies; thus, a comprehensive metabolic profile has not been developed in the rat.

Fluosol or Hespan haemodilution appeared to cause only minor alterations in renal function as measured by urine volume, flow, and pH (Table 4). In another report (Shrewsbury 1986), renal creatinine clearance, used to approximate glomerular filtration rate (GFR), was 5·1–6·6 mL min^{-1} kg^{-1} in Fluosol haemodiluted rats, and did not significantly vary from control animals. Thus, a relatively stable renal physiology appears to exist after Fluosol and Hespan haemodilution, and variations in sulphadimidine disposition due to diuresis, urine pH, and urine flow should be minimal (Vree et al 1980; Weber & Hein 1985). However, excretion and k_u

Table 4. Averaged urinary excretion volumes, flow and pH after haemodilution with 40 mL kg^{-1} of Fluosol or Hespan.

	Treatment groups								
	24 h			48 h			72 h		
	Control	Hespan	Fluosol	Control	Hespan	Fluosol	Control	Hespan	Fluosol
Volume (mL/24 h)	19·9 (2·3)	16·6 (2·7)	15·1* (2·8)	17·5 (3·1)	13·3 (5·0)	17·1 (6·6)	20·2 (5·2)	16·3 (3·9)	22·4 (6·5)
Flow (mL h^{-1})	0·83 (0·10)	0·69 (0·11)	0·63* (0·12)	0·73 (0·13)	0·56 (0·21)	0·71 (0·27)	0·84 (0·22)	0·68 (0·16)	0·94 (0·27)
pH	7·1 (0·2)	7·0 (0·0)	7·0 (0·4)	6·8 (0·3)	6·8 (0·3)	7·0 (0·0)	7·1 (0·4)	6·9 (0·2)	7·2 (0·3)

Mean (s.d.). * Significantly different from corresponding control ($P \leq 0·05$).

were significantly decreased in the 72 h control group. This may indicate that cannulation for 72–96 h alone may have some influence on renal function, but the parameters evaluated in this report did not indicate such a decreased function.

Since renal function appeared to be stable, the changes in k_u and CL_R after Hespan haemodilution are probably due to an inhibition of a secretory process or a change in GFR secondary to a change in plasma protein binding. A change in a secretory process would probably have minimal impact on CL_R since secretion is a minor contributor to CL_R; CL_R was considerably less than GFR in all groups, indicating that tubular reabsorption of sulphadimidine is the predominant contributor. A change in GFR secondary to changes in plasma protein binding seems more likely, but the effect may be quite complex. Both sulphadimidine and acetylsulphadimidine bind to albumin, with the metabolite having a greater affinity for the one specific binding site (Tsang & Thiessen 1989). Albumin concentrations decline as a consequence of haemodilution, and these concentrations remain depressed for 72 h after Fluosol haemodilution (Shrewsbury 1991). Thus, whereas increased free fractions of both compounds would be expected after haemodilution, acetylsulphadimidine competes with sulphadimidine for the specific albumin binding site (Tsang & Thiessen 1989), and there is the possibility that either drug or metabolite may bind to the haemodiluents. Whatever the extent of these opposing factors, the overall effect was minimal on V_d which is influenced by alterations in the free fractions (Gibaldi & McNamara 1978).

Sulphadimidine undergoes nonmicrosomal hepatic acetylation (Zidek & Janku 1979, 1981). Some studies have concluded that hepatic acetylation occurs in the parenchymal cells (Suolinna 1980; DuSouich & Courteau 1981; Olsen et al 1981) while others state that acetylation occurs in the reticuloendothelial system (RES) (Zidek et al 1977; Svensson & Knowlton 1989). Zymosan, a RES stimulant, has been shown to enhance or have no effect on sulphadimidine acetylation in rats (Suolinna 1980). In rabbits, the RES stimulant, Freund's adjuvant, increased sulphadimidine acetylation while two RES depressants, colloidal carbon and cyclophosphamide, had little or no effect (DuSouich & Courteau 1981).

PFCs are taken up by the RES (Tsuda et al 1989) and suppress the RES function when measured by colloidal carbon clearance (Lutz & Metzenauer 1980; Lutz et al 1982; Lutz 1983) and human red blood cell clearance (Castro et al 1984). The RES suppression was found to be cyclic and dose dependent when measured by colloidal carbon clearance (Lutz & Metzenauer 1980; Lutz 1983). If acetylation occurs in the RES, there is no evidence from this report that Fluosol suppressed the RES and thereby sulphadimidine acetylation. If acetylation occurs in the parenchymal cells, then Fluosol emulsion droplets or one of its components must enter the hepatocytes. It has been proposed that the emulsion droplets are freed from their surfactant coating in the RES, and then PFCs and the other constituents move into tissues based on their lipophilicity and other physicochemical properties (Tsuda et al 1989).

In the only other report of sulphadimidine disposition in Fluosol haemodiluted rats (Kemner et al 1984), sulphadimidine was intravenously administered (4·6 mg kg^{-1}) immediately after Fluosol haemodilution. The rats remained under light anaesthesia for 6 h after haemodilution, and periodic blood samples were taken during that time. The animals were then allowed to recover from anaesthesia, and additional blood samples were collected at 24, 48 and 72 h. In that study, CL was unchanged, V_d increased almost 3-fold, and the dependent $t_{\frac{1}{2}}$ more than doubled. However, it is difficult to unify this previous study with the current report since the study designs are so different.

Many mechanisms may be involved in the influence of Fluosol haemodilution on sulphadimidine acetylation. Two of the mechanisms have neither direct nor indirect data to support them; Fluosol haemodilution may increase the availability of acetyl-CoA cosubstrate or alter the turnover rate of *N*-acetyltransferase. Two other mechanisms have some indirect support from studies using Fluosol. There may be an enhanced activity of *N*-acetyltransferase as part of an increased liver mass. Liver weight was increased approximately 18% over 7 days after Fluosol haemodilution (Shrewsbury et al 1987b; Armstrong & Lowe 1989). Another mechanism may involve a change in the blood flow distribution within the liver after haemodilution, a phenomenon known to occur in many organs after haemodilution. Such redistributions may bring sulphadimidine into areas of high *N*-acetyltransferase activity as the result of haemodilution. Acetylation capacity has been found to be twice as great in Sprague-Dawley rat liver and kidney than lung and gut mucosa (Dubbels et al 1980). Detailed perfusion studies of each organ are required for a complete understanding of the influence of Fluosol on sulphadimidine acetylation.

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