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Influence of Moderate Haemodilution with Fluosol or Normal Saline on Carbaryl Disposition in Sprague–Dawley Rats

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Abstract

In rats carbaryl undergoes extensive biotransformation involving both albumin-mediated hydrolysis and cytochrome P-450-mediated metabolism; studies have suggested that approximately one-half of a carbaryl dose is hydrolysed and one-half is metabolized. Fluosol is known to be an inducer of cytochrome P-450, and Fluosol haemodilution reduces plasma albumin concentrations.

The disposition of carbaryl was, therefore, determined in rats for 72 h after 40 mL kg^{-1} haemodilution with Fluosol or normal saline (0·9% NaCl). Volumes of distribution were significantly reduced after saline haemodilution for 72 h but only at 48 h after Fluosol haemodilution. Fluosol and saline haemodilution had little influence on carbaryl total body clearance (CL).

These results indicate that both hepatic and non-hepatic clearance pathways were not influenced by the haemodiluents or the haemodilution procedure.

Carbaryl (1-naphthol-*N*-methylcarbamate, Sevin) is a broad-spectrum pesticide with relatively low mammalian toxicity. It is a member of the class of insecticides known as the methylcarbamates; other carbamates are physostigmine and neostigmine. Carbaryl and other carbamates in this class have been termed 'reversible' or at least 'pseudo-reversible' because the dissociation and regeneration of carbamylated acetylcholinesterase leads to completely regenerated acetylcholinesterase in a short period of time.

Several dispositional studies have been conducted using radiolabelled carbaryl; carbaryl has been labelled at the carbonyl (Hassan et al 1966; Houston et al 1974; Falzon et al 1983; Waldron & Abdel-Rahman 1986), methyl (Hassan et al 1966; Pipy et al 1981; Fernandez et al 1982; Knight et al 1987), or ring (Marshall & Dorough 1979; Tanaka et al 1980; Strother & Wheeler 1980) to investigate the various contributions of hydrolytic and non-hydrolytic pathways to carbaryl disposition. All the labelled studies (carbonyl, ring, methyl) suggest that approximately one-half of a carbaryl dose undergoes non-hepatic elimination (renal excretion, albumin hydrolysis, chemical hydrolysis), and the remainder undergoes hepatic metabolism. The amount of unchanged carbaryl recovered in urine is less than 1% (Houston et al 1974), and biliary enterohepatic cycling plays a major role in the disposition of radioactivity.

In rats, carbaryl also undergoes extensive biotransformation involving both enzymatic hydrolysis and cytochrome P-450-mediated metabolism. Carbaryl is hydrolysed to 1-naphthol by microsomal and cytosolic esterase enzymes in the liver, lung and skin, and cytosolic esterases in the plasma and lysed red blood cells (McCracken et al 1993). 1-Naphthol is further conjugated to 1-naphthyl glucuronide and 1-naphthyl sulphate (Knaak et al 1965). Carbaryl has been found to bind exclusively to albumin in rats, rabbits and man (Casida & Augustinsson 1959; DeBerardinis 1982).

The major metabolic pathway of carbaryl in the liver involves hydroxylation followed by conjugation (McCracken et al 1993). Identified metabolites include 1-naphthylmethylcarbamate *N*-glucuronide, 1-naphthylmethylimidocarbonate *O*-glucuronide, 4-hydroxycarbaryl, 4-(methylcarbamoyloxy)-1-naphthyl glucuronide, 4-(methylcarbamoyloxy)-1-naphthyl sulphate, 5-hydroxycarbaryl, 5-(methylcarbamoyloxy)-1-naphthyl glucuronide, 5-(methylcarbamoyloxy)-1-naphthyl sulphate, 1-naphthyl-*N*-hydroxymethylcarbamate and 5,6-dihydro-5,6-dihydroxy-carbaryl (Dorough et al 1963; Knaak et al 1965; Oonnithan & Casida 1968; Strother 1972; Knight et al 1986, 1987).

Moderate Fluosol haemodilution has been reported to induce the same cytochrome P-450 isoenzymes (P4502B1, P4502B2) induced by phenobarbital in rats (Shrewsbury & White 1990; Shrewsbury 1992). Likewise, haemodilution has been shown to reduce plasma albumin concentrations (Shrewsbury 1991). This study was, therefore undertaken to determine the influence of partial Fluosol haemodilution on the disposition of carbaryl, a drug whose disposition is uniquely dependent on two processes influenced by the haemodiluent. Normal saline haemodilution was included in the study design to demonstrate the influence of haemodilution alone without any influence from the presence of Fluosol.

Materials and Methods

Fluosol was donated by Alpha Therapeutic Corporation (Los Angeles, CA) and prepared as directed within 0·5 h of use. For intravenous administration a solution of carbaryl (3 mg mL^{-1}) was prepared in propylene glycol because carbaryl is insoluble in water (Pipy et al 1981). HPLC solvents, chemicals, intravenous fluids and animals were obtained from commercial vendors. Carbaryl was donated by the Agri-

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cultural Division of Union Carbide Corporation (Research Triangle Park, NC).

Male Sprague–Dawley albino rats, 322 ± 34 g (mean ± s.d.) were allowed free access to food and water. Animals were cannulated and haemodiluted as previously described (Shrewsbury 1986) with 40 mL kg^{-1} Fluosol or saline (0·9% NaCl). The rats received a 6 mg kg^{-1} intravenous dose of carbaryl 0·5, 24, 48 and 72 h after haemodilution. One group of rats, serving as controls, were not exchanged. The group designations are control for the control group, and 0·5HF, 24HF, 0·5HS, 24HS, etc for the time (h) that the animals received the carbaryl dose after either Fluosol (F) or saline (S) exchange.

Blood samples (0·25 mL) were collected in heparinized polypropylene tubes 5, 10, 20, 30, 45, 60, 90, 120 and 150 min after carbaryl administration, and the plasma was harvested and frozen until assayed. To 0·1 mL plasma an equal volume of methanol was added and the sample was centrifuged at 12 000 rev min^{-1} for 10 min to precipitate proteins. Various volumes of the supernatant were analysed by HPLC.

Carbaryl concentrations were determined with a 250 × 4·6 mm i.d. column containing 10 μM C_{18} (Alltech); the mobile phase was 27:73 acetonitrile–0·005 M sodium acetate, pH = 7·0. The column temperature was maintained at 28°C with a column heater; the mobile-phase flow-rate was 1·4 mL min^{-1}. Absorbance was monitored at 220 nm (0·005 AUFS) and the peak height of carbaryl was determined by use of an integrator. Heights were normalized to a 0.2 mL injection. Standard curves prepared using plasma from non-exchanged animals or rats exchanged with fluosol or saline (as appropriate) were linear from 100–6400 ng mL^{-1}. Three hundred and fifty eight plasma samples were analysed in this study. A Proc Univariate analysis (SAS Institute, Cary, NC) indicated that eight of these samples were outliers. To support better compatibility with normal distributions, each outlier was trimmed to a value that was the sum of the highest non-outlier plus twice the difference between the two highest non-outliers.

A one- or two-compartment pharmacokinetic model was fit to the plasma concentration–time data using the non-linear regression program NLIN from SAS. Plasma concentrations were weighted by their reciprocal squared because the coefficient of variation was dependent upon the concentration assayed. Parameter estimates from the fitted data were subsequently used to calculate carbaryl half-life ($t_{\frac{1}{2}}$), clearance (CL) and volume of distribution (Vd) or steady-state Vd (Vd_{ss}). The significance of differences between groups was assessed with Wilcoxon Rank Sums (normal approximation) with a probability of $P \leq 0.05$ considered statistically significant.

Results

Table 1 reports the haematocrits before any exchange (pre-exchange) or before administration of carbaryl (pre-dosing). In all cases where data were obtained, haemodilution significantly reduced the haematocrit; the averaged reduction in the groups was 46·5% (range 35·3–61·0%). The pre-exchange and pre-dosing haematocrits in the control group were identical because that group was not haemodiluted.

Mean times and plasma concentrations were determined for each treatment group (Figs 1 and 2) and the averaged data were fitted with a one- or two-compartment model to obtain initial estimates of the pharmacokinetic parameters. The Akaike information criterion (AIC) was used to determine which compartmental model best described the data (Akaike 1976). The pharmacokinetic parameters obtained served as initial estimates for each treatment group. The individual pharmacokinetic parameters were obtained for each rat, again using a one- or two-compartment model as determined by the AIC. If a one-compartment model best described the data, then Vd was the volume of distribution calculated. If a two-compartment model as indicated, then Vd_{ss} was calculated. The averaged pharmacokinetic parameters are presented in Table 2.

Total body clearance (CL) values in all groups except 24HF were not significantly different from control. The volumes of distribution (Vd/Vd_{ss}) were statistically reduced in several of the later groups (48HF, 24HS, 48HS, 72HS); all of the reductions were approximately one-half the control volume. Statistically significant changes in $t_{\frac{1}{2}}$ were found only in the groups that had significant changes in Vd/Vd_{ss} suggesting that alterations in Vd/Vd_{ss} accounted for the changes in the dependent parameter $t_{\frac{1}{2}}$.

Table 1. Haematocrit values for the various animal groups before any exchange (pre-exchange) or before carbaryl administration (pre-dosing).

Group	Pre-exchange haematocrit	Pre-dosing haematocrit
Control	30·4 ± 6·9	30·4 ± 6·9
Haemodilution with Fluosol		
0·5 h	35·2 ± 4·8	22·2 ± 4·7*
24 h	41·0 ± 5·2	16·0 ± 4·9*
48 h	34·1 ± 5·1	22·0 ± 1·1*
74 h	34·7 ± 5·0	19·6 ± 6·9*
Haemodilution with saline		
0·5 h	36·8 ± 4·0	19·2 ± 2·9*
24 h	33·9 ± 3·6	20·0 ± 4·0*
48 h	47·1 ± 1·4	18·7 ± 3·2*
72 h	38·4 ± 4·0	ND

Data are means ± s.d., n = 5. *$P < 0.05$ compared with corresponding pre-exchange values.

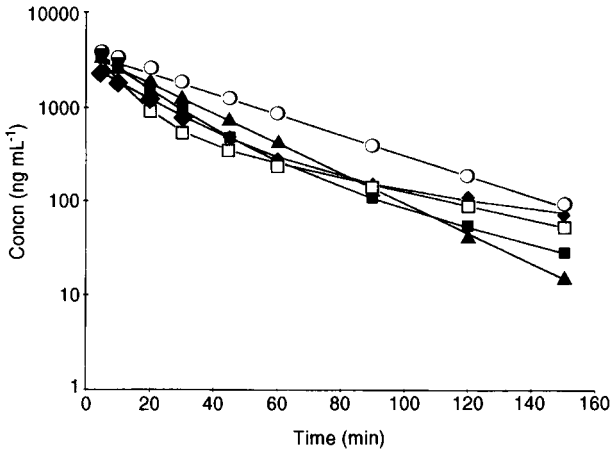

FIG. 1. Mean time and plasma–concentration data for rats haemodiluted with Fluosol. The fitted lines were generated from the one- or two-compartment model which best described the data. □ Control, ● 0·5, ○ 24, ▲ 48, ■ 72 h.

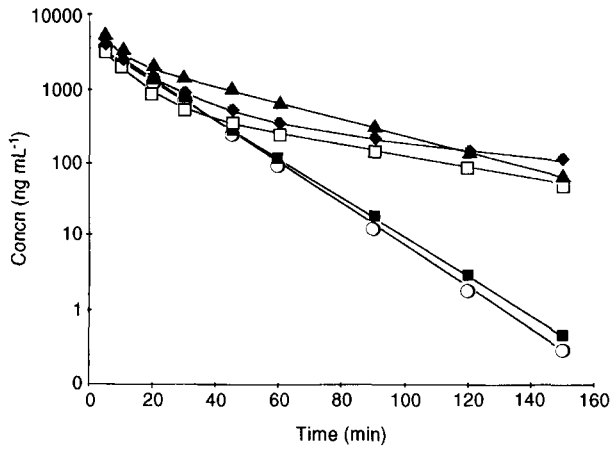

FIG. 2. Mean time and plasma concentration data for rats haemodiluted with saline. The fitted lines were generated from the one- or two-compartment model which best described the data. □ Control, ◆ 0·5, ○ 24, ▲ 48, ■ 72 h.

Discussion

The dose of carbaryl administered in this study was 6 mg kg^{-1}, well below toxic doses. Oral LD50 values of 510 mg kg^{-1} (Carpenter et al 1961) and 600 mg kg^{-1} (Coulston & Serrone 1969) have been reported. Oral or intraperitoneal doses of 100 mg kg^{-1} did not cause esterase inhibition or clinical signs of cholinergic poisoning (Ehrich et al 1992). DeBerardinis (1982) provided evidence that the K_m value for plasma-mediated carbaryl hydrolysis was over 300 μg mL^{-1}; carbaryl plasma concentrations after the 6 mg kg^{-1} dose ranged between 100 and 6400 ng mL^{-1}. The dose used in this study should not, therefore, interfere with esterase activity nor should these hydrolytic enzymes be saturated.

The exchange procedure reduced the haematocrit by approximately one-half, suggesting 50% blood exchange (Table 1). The haematocrit remained depressed throughout the 72 h after exchange with either haemodiluent. These results are consistent with other studies conducted in our laboratory (Shrewsbury 1986, 1987; Shrewsbury et al 1987a, 1987b).

Table 2 shows the averaged pharmacokinetic parameters obtained from the individual fittings. As expected, some data were best described by a one-compartment fit; the remainder of the data required the two-compartment fit. The pharmacokinetic parameters for the control group were CL = 87·2 mL min^{-1} kg^{-1}, Vd_{ss} = 2088 mL kg^{-1} and $t_{\frac{1}{2}}$ = 32·6 min. Several studies have been published on the pharmacokinetics of carbaryl in rats, but most used anaesthetized animals (Houston et al 1974; Pipy et al 1980; Cambon et al 1981; DeBerardinis 1982; Fernandez et al 1982). From those studies, carbaryl $t_{\frac{1}{2}}$ ranged from 31·7 to 137 min, CL ranged from 28·4 to 49·1 mL min^{-1} kg^{-1} and Vd_{ss} was reported to be 976 mL kg^{-1} in one study. In one study in which carbaryl was administered intravenously to conscious animals, $t_{\frac{1}{2}}$ = 77 min, V_β (which is larger than Vd_{ss}) = 5400 mL min^{-1} and CL = 46 mL min^{-1} kg^{-1} (Ehrich et al 1992). The authors indicated that sampling was limited and that the plasma-concentration curves were not well characterized. In isolated perfused rat liver, carbaryl was found to have an intrinsic clearance of 180 mL min^{-1} (flow rate 20 mL min^{-1}) and a predicted extraction ratio of 88% (Ward et al 1988). Comparing all these data with those from the control group in this study is difficult because of the complications of anaesthesia, incomplete data collection and in-vitro model estimates. The control values appear reasonable in the light of literature information, however.

Table 2 also shows that CL was essentially unchanged in all groups except the 24HF group. Fluosol has been shown to induce the same rat isoenzymes (P4502B1 and P4502B2) as phenobarbital (Shrewsbury & White 1990; Shrewsbury 1992). Phenobarbital, however, appeared to have little influence on carbaryl metabolism (Knight et al 1987). It was, therefore, expected that Fluosol or saline haemodilution would have little effect on carbaryl elimination via the cytochrome P450 system. It has previously been reported (Shrewsbury 1992) that drug clearance is depressed soon after haemodilution but has returned to control levels by 72 h. Suggested 'transitory phenomena' include: Fluosol enhancement of hepatic drug uptake via solubilization or adsorption; Fluosol-mediated changes in the sinusoidal plasma membrane permeability; Fluosol-mediated changes in the hepatic microcirculation; Fluosol-mediated release of an endogenous substance secondary to haemodilution; or Fluosol-induced changes in metabolite disposition. There is one additional possibility that might be present in this study. Carbaryl has been shown to block the reticuloendothelial system (Pipy et al 1980, 1981,

Table 2. Averaged pharmacokinetic parameters estimated from individual time and plasma–concentration data.

	Clearance (mL min^{-1} kg^{-1})	Volume of distribution/volume of distribution at steady-state (mL kg^{-1})	Half-life (min)
Control	87·2 ± 31·2	2088 ± 425	32·6 ± 18·7
Haemodilution with fluosol			
0·5 h	94·8 ± 36·0	2108 ± 490	17·6 ± 6·3
24 h	34·8 ± 11·2*	1934 ± 645	45·8 ± 27·5
48 h	61·5 ± 17·9	1084 ± 218*	13·3 ± 5·2*
72 h	69·1 ± 14·4	1485 ± 284	18·9 ± 8·5
Haemodilution with saline			
0·5 h	76·1 ± 23·9	2510 ± 1057	27·0 ± 15.8
24 h	93·3 ± 41·5	1212 ± 442*	9·5 ± 2·8*
48 h	46·9 ± 16·0	1151 ± 154*	23·2 ± 10·7
72 h	106·1 ± 74·9	1331 ± 435*	10·8 ± 3·2*

Data are means ± s.d., n = 5. *$P < 0.05$ compared with control.

1982, 1983). Fluosol elimination is mediated by RES uptake (Ravis et al 1991). Thus carbaryl could block the RES uptake of Fluosol, resulting in animals that are similar to the control group in terms of their hepatic activity. Such a block would necessarily be minimal at 24 h. Each of the above possibilities is speculative at this time; additional studies are required to establish which mechanism(s) would be responsible for the observed data.

Figs 1 and 2 show the mean carbaryl plasma concentration profiles at various times after haemodilution with Fluosol or saline. The pharmacokinetic model needed to describe these profiles changed as a function of time after haemodilution. A similar change in disposition pattern as a function of time has been reported for lignocaine and digoxin in dogs (Hoke 1989; Hoke & Ravis 1989); the changes were attributed to alterations in the volumes of distribution owing to protein-binding changes secondary to an acute release of alpha-1-acid glycoprotein (AAG). It is also known that Fluosol haemodilution reduces plasma albumin concentrations for 72 h (Shrewsbury 1991). The impact of an acute AGG release or reduced albumin concentrations on carbaryl pharmacokinetics would require further investigation and were beyond the scope of this study. It would seem, however, that these factors would certainly influence carbaryl disposition in the light of its high ($\sim 80\%$) plasma-protein binding (Skalsky & Guthrie 1978). A significant finding of the study was that carbaryl volumes of distribution decreased significantly (by half) after saline haemodilution in groups 24HS, 48HS and 72HS. Saline haemodilution was found not to reduce plasma albumin concentrations after 40 mL kg^{-1} haemodilution (Shrewsbury 1991). Likewise, changes in the volumes of distribution after saline haemodilution have had a pattern different from that after Fluosol haemodilution for a number of drugs (Shrewsbury 1986, 1991; Shrewsbury et al 1987a, 1987b). It is not clear why these differences exist, but, as previously postulated, saline haemodilution must elicit a totally different haematological response from Fluosol haemodilution.

Changes both in the hepatic and hydrolytic pathways appear to be minimal because carbaryl CL was essentially unchanged after haemodilution. The significant reductions in Vd/Vd_{ss} might have been expected to substantially alter the hydrolytic pathway's contribution to disposition of carbaryl. For example, Fluosol might inhibit the catalytic activity of albumin or change the conformation of the binding site on the protein. Or Fluosol might preferentially bind carbaryl making it unavailable for albumin hydrolysis. Because saline haemodilution had little influence on CL, and saline was not expected to inhibit the catalytic albumin activity or bind carbaryl, however, such factors were probably of minimal importance.

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