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The relationship between chemical structure and the in vivo metabolism of an homologous series of n-alkyl carbamates

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The metabolism and pharmacokinetics of carbonyl [^{14}C] labelled ethyl, *n*-butyl, *n*-hexyl and *n*-octyl carbamates has been examined in rats after oral and intravenous administration. Hydrolysis of the carbamate group was a major metabolic fate, particularly of the more water soluble carbamates. Conversely, with increasing lipophilicity increasing amounts of ω-1 oxidation products were found both in plasma and urine. The plasma pharmacokinetic data could not be explained by a simple bi-exponential model, ethyl carbamate in particular showing unexpectedly persistent blood levels. A model has been proposed to explain the pharmacokinetic data for ethyl, *n*-butyl, *n*-hexyl and *n*-octyl carbamates. The essential features of this model are that carbamate is thought not to be in equilibrium between the peripheral and central compartment and that hydrolytic metabolism takes place in the peripheral compartment while oxidative metabolism to urinary metabolites occurs in the central compartment.

The aliphatic carbamates (C_2 – C_{10}), which have anaesthetic properties, have proved to be a valuable series of compounds with which to examine the effects of lipophilicity on drug absorption (Houston et al 1974a,b; Wood et al 1978; Bridges et al 1979) and on cytochrome P-450 and albumin binding (Al-Gailany et al 1978; Sargent et al 1982; Wilson et al 1972). These studies have demonstrated that the lipophilicity of a drug may be an important determinant of its pharmacokinetic behaviour. Limited attention has been given to the influence of drug lipophilicity on the overall pharmacokinetics in vivo.

Watanabe & Kozaki (1978) showed that for certain basic compounds their apparent volume of distribution remained constant for those with a low partition coefficient but increased with partition coefficent above a certain threshold value.

Many studies have been made of the carbamate pesticides (e.g. Houston et al 1974c) but with the exception of ethyl carbamate (urethane) the metabolic fate of aliphatic carbamates has been largely ignored. In the present paper the relationship between structure, lipophilicity, metabolic fate and excretion of ethyl, n-butyl, n-hexyl and n-octyl carbamates in the rat is examined.

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MATERIALS AND METHODS

[^{14}C] Carbamates were synthesized in the Chemistry Division, Chemical Defence Establishment, Porton Down. All were shown to be pure by gas liquid chromatography, t.l.c. and melting point. Partition coefficients were measured between octan-1-ol 0·1M phosphate buffer pH 7·4 at 37° (Houston et al 1974).

Animals. Male Wistar rats (300 g) Porton strain were used. The rats were allowed free access to diet (PRD, Christopher Hill Group Ltd) and water throughout the experiments. Animals were housed in Metabowl cages for the collection of urine, faeces and $^{14}CO_2$. Rats were dosed intravenously (5 μmol kg^{-1}) via the femoral vein, with a solution in 0·9% NaCl (saline) of each carbamate. Intraduodenal dosing was carried out using a syringe with a long blunt ended needle. Plasma levels of the parent compounds and of total radiolabelled metabolites were followed by sampling heparinized blood (0·4 ml) from the right carotid artery and centrifuging this to obtain plasma.

Determination of metabolites

$^{14}CO_2$ was trapped in a mixture of ethanolamine–2-ethoxyethanol (1:2). Aliquots of this were taken and radioactivity measured by liquid scintillation.

The metabolites of n-hexyl [^{14}C] carbamate were identified by dosing rats intraperitoneally with this compound dissolved in polyethylene glycol 300 at

0·7 nmol mg^{-1}. After 3 h the rats were exsanguinated from the abdominal aorta under diethyl ether anaesthesia. This blood was immediately heparinized and centrifuged and the plasma fraction was separated and shaken with four changes of 2 volumes of diethyl ether. The pooled ether extracts were dried with anhydrous sodium sulphate and subjected to rotary evaporation at 20°C and 260 mmHg. The residue was applied to a t.l.c. plate and run in chloroform–butan-1-ol(9:1v/v). Spots were eluted with diethyl ether and stored desiccated under nitrogen at −20°C. Chemical ionization mass spectra were recorded on a V. G. Micromass 7079F mass spectrometer using isobutane as the ionizing gas; inlet temperature 50–60°C; source temperature 200°C; source pressure 10^{-4} Torr; ionization voltage 70 eV, acceleration voltage 4000 V. To examine for possible covalently binding of metabolites the blood cell fraction and the precipitated plasma proteins remaining after ether extraction were washed extensively with phosphate buffer and their radioactivity content determined by scintillation counting.

Table 1. Pharmacokinetic constants for four n-alkyl carbamates.

	Carbamate homologue			
Constant	Ethyl	n-Butyl	n-Hexyl	n-Octyl
F	0·892	0·642	0·522	0·330
1 − F	0·108	0·358	0·478	0·670
t_{lag}(h)	1·01	0·75	0·35	0·25
t_{ss}(h)	3·66	3·00	2·75	3·50
$Rate_{ss}$ (μmol kg^{-1} h^{-1})	1·22	1·07	0·95	0·47
A(μM)	8·5	4·2	4·4	5·6
B(μM)	6·6	1·5	1·7	2·8
α(h^{-1})	−15·06	−5·76	−10.38	−18.48
β(h^{-1})	−0·036	−0·72	−0·60	−2·88
$t_{1/2\beta}$(h)	19·25	0·96	1·16	0·24
k_{12}(h^{-1})	8·40	2·46	5·58	6·78
k_{21}(h^{-1})	6·6	2·04	3·54	8·1
k_{el}(h^{-1})	0·078	2·04	1·92	6·6
V_{dss}(ml kg^{-1})	227	583	650	327
$V_{d\beta}$(ml kg^{-1})	228	748	755	403
AUC(μM h)	184	2·8	3·3	1·3
Σ − 1 values:				
m(h^{-1})	−0·3720	0·5121	−0·4539	−0·4353
m′(h^{-1})	—	—	−0·2159	—
$t_{1/2\Sigma}$(h)	1·86	1·35	1·53	1·59
$t'_{1/2\Sigma}$(h)	—	—	3·21	—
r(n)	−0·995 (10)	−0·999 (9)	−0·999 (7)	−0·995 (11)
r′(n)	—	—	−0·995 (5)	—
c(μmol kg^{-1})	6·37	5·05	3·06	2·0
c′(μmol kg^{-1})	—	—	1·30	—

F: the fraction of the dose of each carbamate which is excreted as $^{14}CO_2$ at time = 24 h.
t_{lag}: the lag time in the excretion of $^{14}CO_2$ during which equilibrium with the tissues occurs, see Fig. 2.
t_{ss}: the time during which steady state excretion of $^{14}CO_2$ occurs, see Fig. 2.
$Rate_{ss}$: the steady state, rate of $^{14}CO_2$ excretion: Rate $_{ss}.t_{ss}$ = F.D where D is the dose (= 5 μmol kg^{-1}).
A: intercept on the y-axis of the distribution phase curve.
B: intercept on the y-axis of the β (elimination) curve.
α: first order rate constant for distribution.
β: first order rate constant for elimination. $C_p = Ae^{-\alpha t} + Be^{-\beta t}$.
$t_{1/2\beta}$: half life for elimination: loge 2/β.
k_{12}: first order rate constant for distribution from the central to the peripheral compartment.
k_{21}: first order rate constant for distribution from the peripheral to the central compartment.
k_{el}: first order rate constant for elimination.
V_{dss}: steady state volume of distribution.
$V_{d\beta}$: pseudo-equilibrium volume of distribution.
AUC: area under the time v. plasma concentration curve.
Σ − 1 values: these all relate to the second phase lines (after the initial lag) in Fig. 3.
m: first order rate constants for excretion of $^{14}CO_2$.
$t_{1/2\Sigma}$: half life for $^{14}CO_2$ excretion: $\log_e 2/m$.
r(n): the correlation coefficient, r, for n values in the regression.
c: the intercept of the (second phase) curves on the y-axis.
The primed values, m′, $t'_{1/2\Sigma}$, r′(n′), c′, refer to the third, terminal, phase of the curve for n-hexyl carbamate.

To ascertain whether covalent binding of metabolites was likely to be a significant fate in the liver each [^{14}C]carbamate was incubated for up to 1 h with rat isolated hepatocytes (Jones et al 1978) and the cell contents examined for the presence of covalently bound metabolites at the end of the incubation by washing in fresh phospate buffered saline twice, resuspending the cells in a small volume of distilled water and sonicating this suspension briefly in a sonic bath. Aliquots of the resulting supension were assayed for their radioactivity content by scintillation counting. Plasma levels of the [^{14}C]carbamates were fitted by a biexponential equation for a two compartment open pharmacokinetic model (Harris & Riegelman 1969). Data for each animal was analysed separately (Table 1).

RESULTS

Plasma concentrations of parent carbamate were determined at various times after the intravenous administration of carbonyl ^{14}C-labelled ethyl, n-butyl, n-hexyl or n-octyl carbamate (5 μmol kg^{-1}) into the femoral vein of male rats. No plasma

metabolites were detected for ethyl carbamate but for the other three carbamates at least two polar metabolites were found. All four carbamates showed a biexponential decline in plasma concentration of parent compound with time (Table 2) which could be described by the equation, $C_p = Ae^{-\alpha t} + Be^{-\beta t}$. For ethyl carbamate the biexponential model did not account completely for the variation of total amount of parent compound in the body with time. It can be seen that the plasma level of ethyl carbamate remained virtually constant after the initial distribution phase, despite the rapid loss of ethyl carbamate as $^{14}CO_2$ (Table 2, Fig. 1). This steady plasma level after the initial distributive phase occurred over a three thousand fold dose level (5 μmol −15 mmol kg^{-1}). No covalent binding to plasma or blood cells could be detected. Nor was any covalent binding of metabolites detectable when the carbamates were incubated with isolated rat hepatocytes.

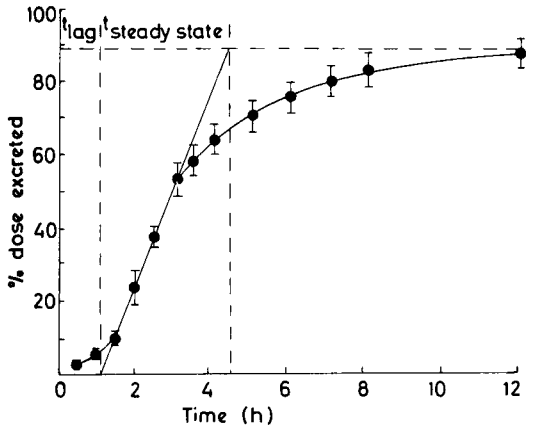


FIG. 1. Excretion of $^{14}CO_2$ (mean with s.d.) following the intravenous injection of [^{14}C]ethyl carbamate 5 μmol kg^{-1}.

After intraduodenal administration the appearance of parent carbamate in the systemic circulation was rapid for all four carbamates showing a peak after about 5 min (e.g. see Fig. 2). After reaching a maximum the plasma levels of each carbamate showed a distinct distributive phase before the terminal phase became apparent. The areas under

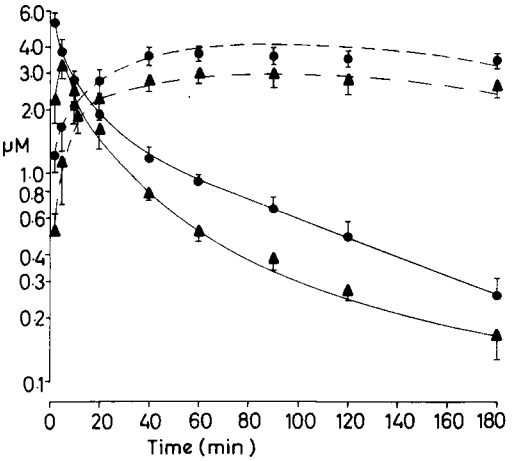


FIG. 2. Plasma concentrations of parent *n*-hexyl carbamate (—) and total radiolabelled metabolites (----) following intravenous (● data points) or intraduodenal (▲) administration of n-hexyl [^{14}C]carbamate to rats 5 μmol kg^{-1}. x-axis: Time (min). y-axis: Plasma concentration of parent compound. n-hexyl carbamate and equivalent concentration of its metabolites. μM.

the curves for ethyl carbamate were similar for both intraduodenal and intravenous routes, however, for n-butyl, n-hexyl and n-octyl carbamates the areas under the plasma concetration-time curves (AUC) between time zero and infinity for the intraduodenal route were significantly lower than those obtained for intravenous administration (i.e. 81% for n-butyl,

Table 2. Comparison of the effects of intravenous and intraduodenal routes of administration on the plasma levels of various aliphatic carbamates (means with s.d.) after 5 μmol kg^{-1}.

Time (min)	Ethyl (μM)		n-Butyl (μM)		n-Hexyl (μM)		n-Octyl (μM)	
	i.v.	i.d.	i.v.	i.d.	i.v.	i.d.	i.v.	i.d.
2	11·4 (1·3)	7·9 (0·3)	5·2 (1·0)	3·1 (0·3)	5·3 (0·6)	2·2 (0·5)	6·1 (1·1)	0·5 (0·2)
5	8·6 (0·5)	8·6 (0·6)	3·9 (0·4)	3·4 (0·3)	3·8 (0·6)	3·3 (0·4)	3·2 (0·3)	1·7 (0·2)
10	7·3 (0·5)	7·8 (0·3)	3·1 (0·4)	2·7 (0·2)	2·8 (0·3)	2·5 (0·3)	2·0 (0·3)	1·3 (0·2)
20	6·7 (0·5)	7·0 (0·3)	1·9 (0·2)	1·7 (0·2)	1·9 (0·1)	1·6 (0·3)	1·2 (0·2)	0·59 (0·06)
40	6·4 (0·4)	6·4 (0·1)	1·1 (0·1)	0·8 (0·1)	1·2 (0·1)	0·8 (0·1)	0·4 (0·1)	0·17 (0·02)
60	6·3 (0·5)	6·2 (0·2)	0·8 (0·1)	0·6 (0·1)	0·9 (0·2)	0·5 (0·1)	0·15 (0·04)	not detected
90	6·2 (0·4)	6·1 (0·2)	0·5 (0·1)	0·41 (0·02)	0·7 (0·1)	0·39 (0·04)	not detected	,,
120	6·1 (0·4)	6·0 (0·2)	0·4 (0·03)	0·32 (0·02)	0·5 (0·1)	0·28 (0·03)	,,	,,
180	5·9 (0·4)	5·9 (0·2)	0·19 (0·05)	0·17 (0·02)	0·26 (0·06)	0·17 (0·04)	,,	,,
$\frac{AUC_{id}}{AUC_{iv}}$	1·0		0·81		0·80		0·45	

i.v. = intravenous. i.d. = intraduodenal. AUC = Area under curve.

80% for n-hexyl and 45% for n-octyl carbamates of the intravenous values, Table 2).

After intravenous or intraduodenal administration of each of the carbamates, negligible amounts of radioactivity (less than 1% of dose) were found in the faeces while the total recovery of the dose from expired air and urine was between 90·8 and 97·1%. The cumulative amounts of radioactivity excreted as CO_2 for each carbamate is shown in Fig. 3. For each carbamate a greater percentage of the dose was recovered in the expired air in 24 h following intravenous dosing than following oral administration. Conversely, for each carbamate the total amount of radioactivity recovered in urine after 24 h was greater following oral administration than following intravenous administration (Table 3).

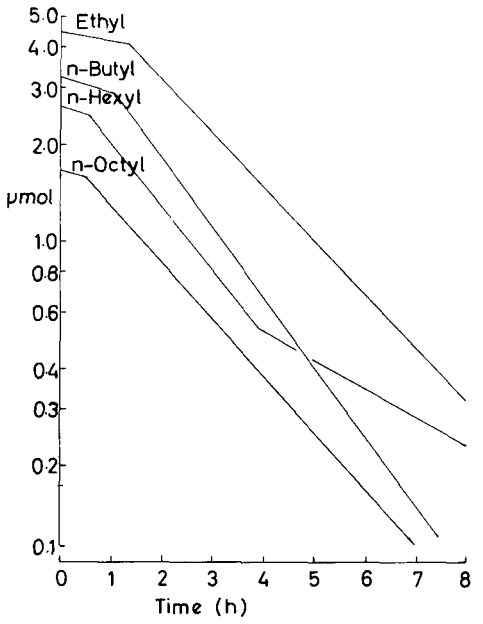


FIG. 3. A.R.E. (amount remaining to be excreted, or Σ − 1) plots of the excretion of $^{14}CO_2$ resulting from the hydrolytic metabolism of four n-alkyl carbamates. Data points have been omitted for the sake of clarity.

For each carbamate t.l.c. of the urine showed that less than 5% of the total urinary radioactivity was associated with parent carbamate.

The mass spectrometer fragmentation pattern for hexyl carbamate metabolites isolated from plasma 3 h after i.p. dosing was consistent with the two major metabolites being the ω-1 hydroxylation product and its further oxidation product, the ketone. Thus the following mass peaks were observed. Suspected (ω-1) hydroxy product: *m/z* 162 (molecular ion), *m/z* 144 (loss of water from molecular ion), *m/z* 101 (breaking ester link to give $CH_3CH.OH(CH_2)_4^+$), *m/z* 43 (CH_3CO^+). Suspected (ω-1) ketone, *m/z* 160 (molecular ion), *m/z* 99 (breaking of ester link to produce $CH_3CO.(CH_2)_4^+$), *m/z* 43 (CH_3CO^+). Identical metabolites were found in urine as judged by mobilities in various t.l.c. systems. Some minor metabolites (< 5% total metabolites) were apparent on the thin layer chromatograms of the more lipophilic carbamates in addition to the two major (ω-1) oxidative metabolites; these were not identified.

Table 3. Excretion of four radiolabelled carbamates 24 h after intravenous or oral administration (5 µmol kg^{-1}).

Carbamate	Route	% Dose recovered as CO_2	% Dose recovered in urine	Total[a] % recovery from CO_2 and urine
Ethyl carbamate	i.v.	89·2 (3·7)	3·3 (1·0)	92·5
	oral	83·6 (4·2)	7·2 (1·8)	90·8
n-Butyl carbamate	i.v.	64·2 (2·8)	29·9 (3·6)	94·1
	oral	60·8 (2·6)	34·6 (2·9)	95·4
n-Hexyl carbamate	i.v.	52·2 (3·1)	44·2 (3·8)	96·4
	oral	42·6 (2·6)	51·3 (3·1)	93·9
n-Octyl carbamate	i.v.	33·0 (3·6)	64·1 (4·3)	97·1
	oral	29·1 (2·9)	66·3 (3·2)	95·4

[a] Less than 1% of any dose recovered in faeces. Results are the means of 3 animals (with s.d.).

$^{14}CO_2$ was a major metabolite of each carbamate. For ethyl carbamate it was the only metabolite detected accounting for 45% of an administered i.v. dose after 3 h. With increasing carbon chain length the ratio of ω-1 oxidative products to carbon dioxide increased (see Fig. 4) from 0·03 for ethyl carbamate to 1·9 for octyl carbamate.

DISCUSSION

The rapid absorption of all four carbamates given intraduodenally is in agreement with the rates of absorption reported by Houston et al (1974a) using the in situ preparation of Doluisio et al (1969).

The similarity of the plasma concentration time profiles for n-butyl and n-hexyl carbamate and the differences shown for n-octyl carbamate and n-ethyl carbamate indicate a parabolic relationship between lipophilicity and pharmacokinetic profile. A similar phenomenon has been observed in a number of biological systems (Hansch & Clayton 1973) including duodenal absorption of carbamates (Houston et al 1974a, b; Houston & Wood 1980).

The influence of route of administration on the elimination of the carbamates was assessed by a comparison of AUC for the plasma concentration-time curves (Harris & Riegelman 1969). This method assumes that the parameters of distribution and elimination remain constant after administration

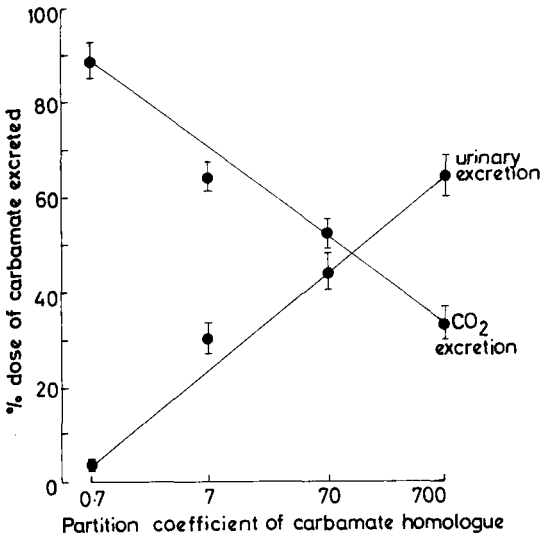


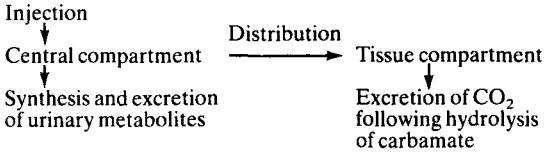
FIG. 4. Relationship of dual pathways for the excretion of n-alkyl carbamates to their partition coefficients. (% excreted, mean with s.d.)

of the same dose by two different routes. Except for ethyl carbamate the areas were found not to be equal and it must therefore be concluded that more parent carbamate reaches the vascular compartment by the intravenous route that by the intraduodenal route. Because only an insignificant percentage of the dose was recovered in the faeces during 24 h this phenomenon is probably not due to incomplete absorption but to metabolism of the carbamates either during absorption or during the first pass through intestinal mucosa and/or liver. Houston et al (1974a) have shown that minimal metabolism of these carbamates occurs in rat gut sac preparations, in contrast, metabolism by hepatocytes is extensive (Sargent et al 1982). Metabolic studies carried out on these carbamates showed that as the chain length of the carbamates was increased, a decrease in metabolic hydrolysis took place (as indicated by the total $^{14}CO_2$ excreted) and this was accompanied by an increase in other metabolic conversions, the products of which were excreted in the urine (Fig. 4). The increasing importance of the non-hydrolytic route of metabolism with increasing chain length is also reflected in the plasma levels of the total radiolabelled metabolites. As the series is ascended the rate of appearance of these ω-1 oxidized metabolites in the plasma increases and so does the peak plasma level attained. A similar observation has been made using isolated rat hepatocytes. Cytochrome P-450 appears to be responsible for this ω-1 oxidative reaction (Sargent et al 1982).

Since ethyl carbamate is very extensively metabolized via hydrolysis but has a very poor binding affinity to cytochrome P-450, it is probable that hydrolysis to produce CO_2 is not cytochrome P-450 dependent. It has been shown (Boyland & Roden 1949; Boyland et al 1963; Nery 1968) that about 5–8% of a dose of ethyl carbamate (urethane) undergoes *N*-hydroxylation which gives rise to various degradation products following its conjugation with glutathione, whereas for butyl carbamate only 0·08% of the dose was *N*-hydroxylated within 24 h (Boyland & Nery 1965). The very poor affinity of ethyl carbamate for the major species of hepatic cytochrome P-450 raises the question as to the enzyme responsible for this *N*-hydroxylation.

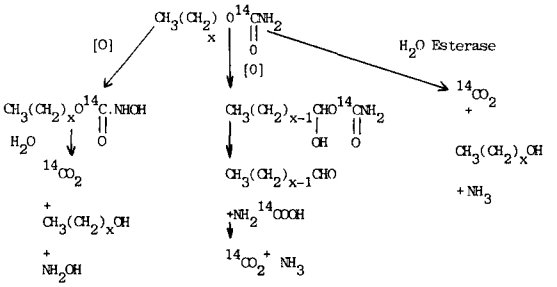
On the basis of the plasma concentration-time curves following intravenous administration, the fate of butyl, hexyl and octyl carbamates can be described by a biexponential equation which is usually interpreted in terms of a two compartment open pharmacokinetic model consisting of a well perfused central compartment and a slowly perfused peripheral or tissue compartment. However, examination of both the plasma level and CO_2 production plots for ethyl carbamate indicated that the usual two compartment open model is not adequate to describe the total pharmacokinetic behaviour of this carbamate. Between the first and third hour after an intravenous dose approximately 45% of the dose was metabolised to CO_2, whereas during the same time the plasma levels of ethyl carbamate remained virtually constant (see Table 1, Fig. 1). If the above model were correct for ethyl carbamate then the plasma levels would be expected to fall markedly during this period as a large proportion of the dose is eliminated.

The failure of ethyl carbamate to fit the usual model may be explained if it is assumed that the production and excretion of $^{14}CO_2$ from ethyl carbamate and other carbamates occurs in a tissue compartment in which the levels of carbamate change independently of any changes in the central compartment and are not reflected by changes in that compartment's (plasma) carbamate concentration:



In support of this concept is the finding that isolated hepatocytes produce only small amounts of CO_2 from each of these carbamates although extensive amounts of ω-1 oxidation products are formed with

the more lipophilic carbamates (Sargent et al 1982). The data for the CO_2 excretion of the four carbamates has been plotted by the 'sigma minus' (Σ-1) method in Fig. 3. It is apparent (from Table 1) that, after an initial lag time, elimination of the four carbamates as CO_2 takes place at virtually the same rate for each of them. This may indicate that they have a single rate limiting pathway for excretion as CO_2 which is common to them all. Possible mechanisms include:



In the metabolism of two *N*-methyl aromatic insecticidal carbamates, landrin and carbaryl, Houston et al (1974c) found rate constants of $-0{\cdot}437$ and $-0{\cdot}3918$ h^{-1} respectively for their elimination as CO_2. These values are similar to those for the *N*-unsubstituted aliphatic carbamates reported here (the values 'm' in Table 1) which suggests the existence of a common hydrolytic pathway.

The lag time before steady state occurs can be seen as the period taken for $^{14}CO_2$ to equilibrate with CO_2 produced by intermediary metabolism (glycolysis, Krebs cycle, etc.), its duration varying inversely with the rate of hydrolysis of the parent carbamate.

Considering the body as whole, the amount of drug remaining varies with time as the sum of these two independent processes:

$$C_p^t \cdot V_{d\beta} + (FD - f)$$

where f is the amount (μmol kg^{-1}) and F is the fraction of the dose excreted as CO_2 at time t, $V_{d\beta}$ is the pseudoequilibrium volume of distribution, D the dose and C_p^t the plasma concentration. In our model it is assumed that the central compartment gives rise almost exclusively to aliphatic chain oxidation products and it is not involved significantly with the excretion of CO_2. This is supported by the observation that the rate constants for exchange between the central and peripheral compartments k_{12} and k_{21} are not significantly different.

The reason for the much greater persistence of ethyl carbamate in the plasma than the other carbamates remains uncertain. It may be related in part to the fact that ethyl carbamate, unlike the other carbamates is not cleared by hydroxylation in the side chain. Since ethyl carbamate itself has a very poor affinity for serum albumin (Wilson et al 1972) a possible explanation is that ethyl carbamate but not the other carbamates forms significant amounts of a labile metabolite which is avidly bound to plasma proteins, this metabolite either being converted back to ethyl carbamate when plasma samples are extracted with diethyl ether or during chromatography. An *N*-oxidized metabolite is a possible candidate for this.

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