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Pharmacokinetics of absorption, distribution and elimination of fenfluramine and its main metabolite in man

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Previously reported data (Beckett & Brookes, 1967) for the excretion of (±)-fenfluramine and its main metabolite, norfenfluramine, have been examined pharmacokinetically using an analogue computer. A three compartment open model was proposed to simulate the biological processes with one peripheral compartment rapidly equilibrating with the central compartment and the second (tissue) compartment only slowly attaining equilibrium. Good agreement between experimental and computed data was obtained, although marked inter-subject variation was recorded. This was attributed to inter-subject differences in the three body compartments. Differences between the pharmacokinetic parameters obtained after oral and intravenous administration of fenfluramine indicated that the drug was significantly *N*-dealkylated in the intestine or on a first-pass through the liver.

Fenfluramine [1-(3-trifluoromethyl phenyl)-2-ethylamino propane] is extensively *N*-deethylated to norfenfluramine in man and the urinary excretion of both these bases is dependent on urinary pH and flow rate (Beckett & Brookes, 1967). These authors controlled urinary pH at acidic values to minimize the reabsorption of drug and metabolite in the kidney tubules and reported urinary excretion data after oral and intravenous administration of (±)-fenfluramine and (±)-norfenfluramine. In the present paper these data are examined using suitable biological models programmed on an analogue computer and the pharmacokinetic interpretations are discussed.

Theoretical

Beckett & Tucker (1968) made several assumptions in designing pharmacokinetic models to describe the biological processing of amphetamine and methylamphetamine and these we have modified slightly; the complete list of assumptions is as follows.

(1) Drug transfer rates from one compartment to another are directly proportional to the concentration or the amount of drug in that compartment, i.e. absorption, transfer from one body compartment to another, metabolism and excretion are apparent first order rate processes with rate constants of reciprocal time.

(2) The rate of urinary excretion of the drug is directly proportional to the concentration of drug in the plasma. This assumption was valid for amphetamine (Beckett, Salmon & Mitchard, 1969).

(3) Compartments are uniform and homogeneous during the transfer process.

(4) There is no decomposition of the drug at the absorption site.

(5) The rate constant for drug absorption is not influenced by the position of the drug in the gastrointestinal tract.

(6) The drug is completely absorbed by all routes of administration.

(7) Entero-hepatic or salivary recycling, diffusion from plasma into the stomach and renal tubular reabsorption of the drug are not significant.

(8) Excretion of the drug by pathways other than the kidney is negligible.

Pharmacokinetic models (*see appendix for rate equations and diagrams*)

Pharmacokinetic studies with amphetamine (Beckett & Tucker, 1966, 1968; Beckett, Boyes & Tucker, 1968a, b; Beckett, Salmon & Mitchard, 1969), methylamphetamine (Beckett & Tucker, 1968) and ephedrine (Wilkinson & Beckett, 1968) assumed the body to be a single homogeneous compartment. This assumption was justifiable for the above drugs since single exponential falls in the rate of excretion against time plots were recorded. However, data obtained after administration of fenfluramine and norfenfluramine (Beckett & Brookes, 1967) revealed bi- and tri-exponential decays after oral and intravenous administration, respectively. This indicated that a three compartment open model was a minimal requirement to simulate the distribution of these drugs in the body. The theoretical basis of pharmacokinetic models containing two compartments (Riegelman, Loo & others, 1968a, b; Loo & Riegelman, 1968; Rowland, Riegelman & Epstein, 1968; Gibaldi, Nagashima & Levy, 1969; Rowland, Benet & Riegelman, 1970; Kaplan, 1970; Kaplan, Weinfield & others, 1970), three compartments (Garrett, Thomas & Wallach, 1960; Garrett, Johnston & Collins, 1962, 1963; Garrett & Alway, 1963; Nagashima, Levy & O'Reilly, 1968; Gibaldi & Feldman, 1969; Levy, Gibaldi & Jusko, 1969) and multi-compartments (Matthews, 1967; Nodine, 1970) has been reported.

Beckett & Brookes (1967) reported less unchanged drug was excreted in urine after oral than after intravenous administration of norfenfluramine and fenfluramine. This suggested some drug was metabolized significantly on a first-pass through the liver before it reached the general circulation. Similar observations were made with pentazocine (Beckett, Kourounakis & others, 1970) and acetylsalicylic acid (Harris & Riegelman, 1969). The biological models proposed to simulate the pharmacokinetics of norfenfluramine (Model I) and fenfluramine (Model II) were designed to allow for this "first-pass" phenomenon. Thus, drug administered orally is considered to be absorbed into a peripheral compartment (which includes the liver) from which biotransformation occurs, whilst intravenous dose is presented directly to the central (plasma) compartment.

The biological model proposed for the study of the pharmacokinetics of fenfluramine (Model II) also incorporates the distribution and elimination of its main metabolite, norfenfluramine. To study the kinetics of the metabolite, the model should contain similar compartments to those used for the drug to allow examination of the biological processes following administration of norfenfluramine itself. However, because of a limited number of integrators in the analogue computer, only one peripheral compartment was considered when simulating the distribution of norfenfluramine produced as a metabolite of fenfluramine.

METHODS

Trials

Doses of 16·95 mg base (±)-norfenfluramine and 17·28 mg base (±)-fenfluramine were given in aqueous solution orally or intravenously to three healthy male subjects

with maintained acidic urinary pH (4·8 ± 0·2) and the urinary excretions of the drugs were measured (Beckett & Brookes, 1967).

Computer simulations

A PACE TR20R (Electronic Associates Ltd.) analogue computer was used together with an X-Y recorder (Bryans Ltd.) and a digital voltmeter (Roband Ltd.). The appropriate pharmacokinetic model to describe absorption, distribution, metabolism and excretion of the drugs was programmed on the computer. The experimental urinary excretion data were plotted on the X-Y recorder, both as cumulative excretion and rate of excretion. The settings of the rate constant potentiometers were systematically varied in an attempt to fit the computed curve to the experimental data points. When the best fit was obtained, the settings of the rate constant potentiometers were read from the digital voltmeter.

In fitting the norfenfluramine data obtained after administration of fenfluramine, it was assumed that the rate constants describing the distribution and elimination processes of the metabolite had exactly the same values as when norfenfluramine, itself, was administered. The rate constants for all biological processes of both drugs were assumed to be similar after oral and intravenous administration, although some changes in k_m values might be expected between the two routes of administration because of the "first-pass" phenomenon, i.e. the effect of first passage of the drug through the liver on the pattern of its metabolism.

RESULTS AND DISCUSSION

In general, good agreement between the computed and the experimental urinary excretion data of norfenfluramine (Fig. 1) and fenfluramine (Fig. 2) was obtained. Some differences in the profiles can be explained by changes in urine flow rate which is known to affect the rate of excretion of these drugs even under acidic conditions (Beckett & Brookes, 1967). High urine flow rates may decrease reabsorption of drug in the kidney tubules or may induce passive transfer of drug from plasma to kidney tubular fluid. Passive transfer of amphetamine (Beckett, Salmon & Mitchard, 1969) and *p*-chloroamphetamine (Beckett, Salmon & Mitchard: unpublished observations) has been reported. Therefore, the rate constant k_e is a hybrid constant probably combining the effects of glomerular filtration, passive transfer from plasma to kidney tubular fluid and re-absorption from tubular fluid to plasma.

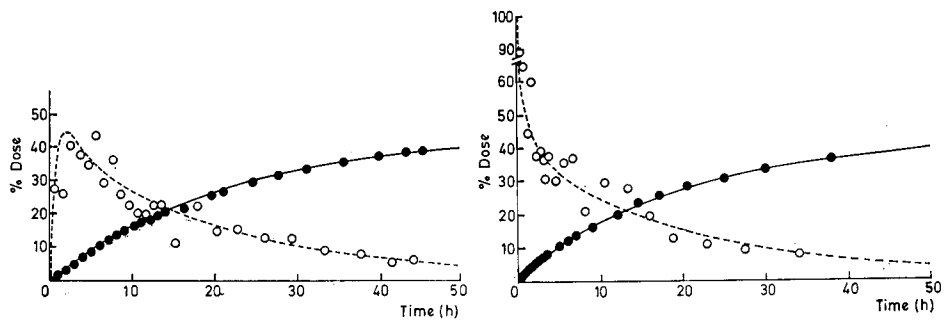


FIG. 1. Computer curves and experimental data points for the urinary excretion of (±)-norfenfluramine after (L) oral (R) intravenous administration of 16·95 mg base (as hydrochloride salt) under conditions of acidic urine. Subject I. ● Experimental points for cumulative urinary excretion (% dose). ○ Experimental points for dU/dt × 20 (% dose/h).

As expected, slight modifications in the values of k_m have to be made after oral administration of norfenfluramine to allow for the first-pass through the liver. However, the other rate constants were the same after both routes of administration (Table 1).

With fenfluramine, only small changes in some of the distribution rate constants had to be made after oral administration in order to obtain a good correlation of experimental and computed data, but significant changes had to be made in k_{m_1} and k_{m_2}

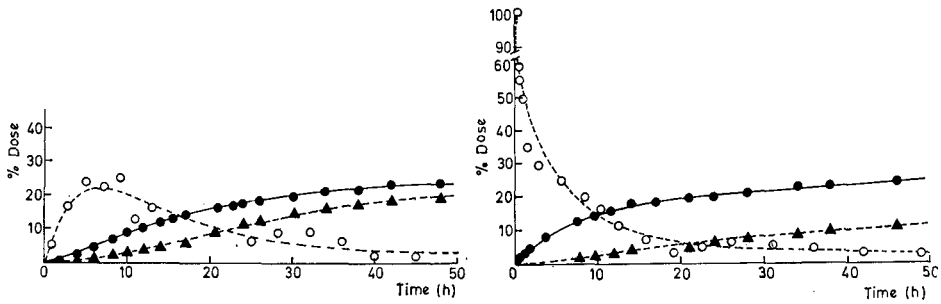


FIG. 2. Computer curves and experimental data points for the urinary excretion of (±)-fenfluramine after (L) oral (R) intravenous administration of 17·28 mg base (as hydrochloride salt) under conditions of acidic urine. Subject I. ● Experimental points for cumulative urinary excretion of fenfluramine (% dose). ○ Experimental points for dU/dt × 20 of fenfluramine (% dose/h). ▲ Experimental points for cumulative urinary excretion of norfenfluramine (% dose).

Table 1. *Pharmacokinetic constants of* (±)-*norfenfluramine.*

	Subject I		II		III	
Rate constants (h^{-1})	Route i.v.	oral	i.v.	oral	i.v.	oral
k_a	—	1·190	—	0·844	—	0·472
k_{m_1}	0·093	0·093	0·100	0·112	0·083	0·099
k_e	0·072	0·072	0·103	0·103	0·062	0·062
k_{12}	3·974	3·794	5·381	5·381	6·045	6·045
k_{21}	3·669	3·669	5·568	5·568	2·978	2·978
k_{13}	0·540	0·540	0·180	0·180	0·022	0·022
k_{31}	0·472	0·472	0·046	0·046	0·038	0·038

(Table 2); k_{m_1} was decreased whilst k_{m_2} was increased relative to the constants obtained after intravenous administration. This indicated that de-alkylation (governed by k_{m_2}) was more extensive after oral than after intravenous administration. Thus, some de-alkylation must occur in a compartment which is not readily available after intravenous administration of the drug. It is therefore, proposed that some de-alkylation occurs in the intestine or during a first-pass through the liver. Since gut-flora are capable of many metabolic processes (Scheline, 1968) these, or enzymes in the intestinal wall, may dealkylate fenfluramine. Data suggesting fenfluramine is de-alkylated in the intestine were supplied by Brookes (1968) who detected norfenfluramine in the gut after administration of fenfluramine. However, although less unchanged fenfluramine was recovered after oral than after intravenous administration of the drug, the difference could not account for all the increase in excretion of norfenfluramine.

Significant inter-subject variations in the pharmacokinetic parameters occurred with both drugs probably due to differences in the volumes of the three body compartments in the volunteers.

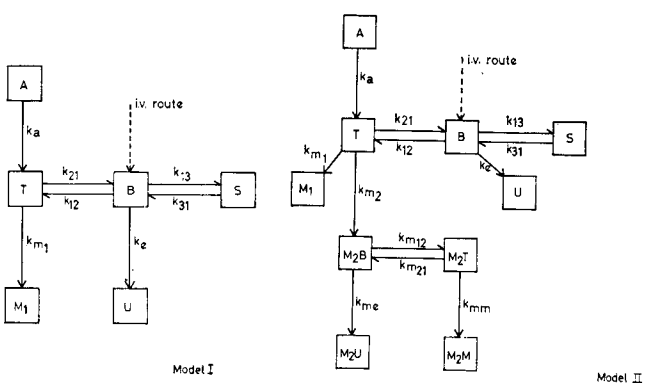
The rate constants (Tables 1 and 2) indicate that the profiles of amount of drug *versus* time in compartments B and T were similar, but compartment S exhibited a slow build up and slower release of drug. Significant amounts of drug remained in compartment S even 48 h after administration. When the amount of drug in S was at a maximum (about 10 h after administration) a steady-state existed; subsequently, the overall kinetics of the system were governed by the rate of release of drug from S.

Table 2. *Pharmacokinetic constants of* (±)-*fenfluramine.*

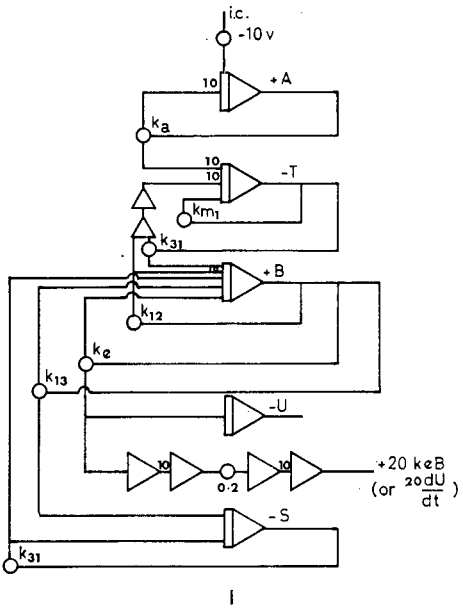
	Subject I		II		III	
Rate constants (h^{-1})	Route i.v.	oral	i.v.	oral	i.v.	oral
k_a	—	0·17	—	0·544	—	0·544
k_{m_1}	0·088	0·025	0·071	0·016	0·040	0·002
k_{m_2}	0·054	0·110	0·063	0·098	0·075	0·198
k_e	0·070	0·070	0·102	0·102	0·034	0·084
k_{12}	7·020	7·020	3·753	3·391	6·045	4·440
k_{21}	4·862	4·862	2·192	2·204	3·036	3·970
k_{13}	0·140	0·140	0·123	0·100	0·202	0·635
k_{31}	0·055	0·055	0·174	0·028	0·378	0·184
k_{mm}	0·093	0·093	0·112	0·112	0·083	0·083
k_{me}	0·072	0·072	0·103	0·103	0·062	0·062
$k_{m_{12}}$	3·974	3·974	5·381	5·381	6·045	6·045
$k_{m_{21}}$	3·669	3·669	5·568	5·568	2·978	2·978

Compartment S would be expected to include the brain, deposits of fat and some tissues with limited blood supplies. This suggestion is supported by the results of Duhault & Fenard (1965) who recorded concentrations of fenfluramine in dog brain markedly higher than those of amphetamine; also, concentrations of fenfluramine in fatty tissues, in general, were much higher than those of amphetamine.

APPENDIX



Biological models for studying the pharmacokinetics of norfenfluramine (Model I) and fenfluramine (Model II)



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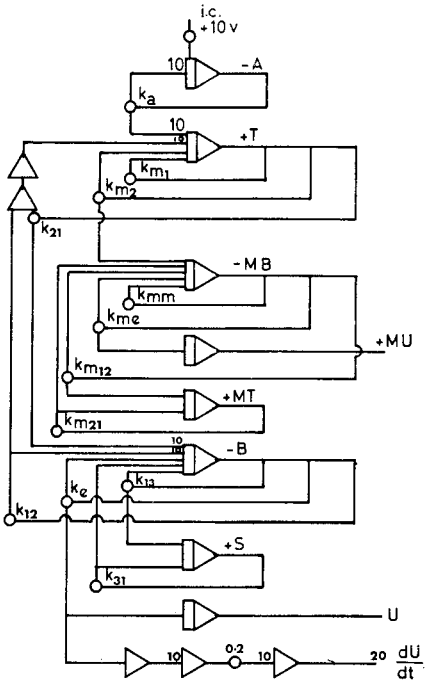

II

Analogue computer program for Models I and II.

Rate equations describing model I:

(a) Oral route: $dA/dt = -k_aA$; $dU/dt = k_eB$; $dM_1/dt = k_{m_1}T$;
$dT/dt = k_aA + k_{12}B - k_{21}T - k_{m_1}T$; $dB/dt = -k_{12}B + k_{21}T - k_{13}B + k_{31}S - k_eB$;
$dS/dt = k_{13}B - k_{31}S$.

(b) Intravenous route: as above except: $dT/dt = k_{12}B - k_{21}T - k_{m_1}T$;
$dB/dt = D - k_{12}B + k_{21}T - k_{13}B + k_{31}S - k_eB$.

The rate equations describing Model II:

(a) oral route: $dA/dt = -k_aA$; $dU/dt = k_eB$; $dM_1/dt = k_{m_1}T$; $dM_2/dt = k_{m_2}T$;
$dT/dt = k_aA + k_{12}B - k_{21}T - k_{m_1}T - k_{m_2}T$; $dB/dt = -k_{12}B + k_{21}T - k_{13}B + k_{31}S - k_eB$;
$dS/dt = k_{13}B - k_{31}S$; $dM_2M/dt = k_{mm}[M_2T]$; $dM_2U/dt = k_{me}[M_2B]$;
$dM_2B/dt = k_{m_2}T - k_{m12}[M_2B] + k_{m_{21}}[M_2T] - k_{me}[M_2B]$;
$dM_2T/dt = k_{m12}[M_2B] - k_{m_{21}}[M_2T] - k_{mm}[M_2T]$,

(b) Intravenous route: As above except: $dT/dt = k_{12}B - k_{21}T - k_{m_1}T - k_{m_2}T$;
$dB/dt = D - k_{12}B + k_{21}T - k_{13}B + k_{31}S - k_eB$.

t	time in h after ingestion of dose
Lag time	the time interval between ingestion of the dose and zero time
Zero time	the time at which loss of drug from the gastro-intestinal tract may be described as a first-order process.
D	the dose
A	the amount of drug in the gastrointestinal tract.
B	the amount of drug in the central compartment.
T	the amount of drug in the peripheral compartment which rapidly equilibrates with B.
S	the amount of drug in the peripheral compartment which slowly equilibrates with B.
U	the amount of unchanged drug excreted in the urine.
M_1	the amount of unspecified metabolites formed.
M_2	the amount of metabolite, norfenfluramine, formed.
M_2B	the amount of metabolite, norfenfluramine, in the central compartment.
M_2T	the amount of metabolite, norfenfluramine, in the peripheral compartment which rapidly equilibrates with M_2B.
M_2U	the amount of metabolite, norfenfluramine, excreted in the urine.
M_2M	the amount of unspecified metabolites formed from the major metabolite, norfenfluramine.
k_a	the rate constant for the absorption of drug from the gastrointestinal tract.
k_{12}	the rate constant for transfer of drug from B to T.
k_{21}	the rate constant for transfer of drug from T to B.

k_{13} the rate constant for transfer of drug from B to S.
k_{31} the rate constant for transfer of drug from S to B.
k_e the rate constant for the excretion of unchanged drug.
k_{m1} the rate constant for an unspecified metabolic route.
k_{m2} the rate constant for the metabolism of fenfluramine to norfenfluramine.
k_{m12} the rate constant for the transfer of metabolite, norfenfluramine, from M_2B to M_2T.
k_{m21} the rate constant for the transfer of metabolite, norfenfluramine, from M_2T to M_2B.
k_{me} the rate constant for the excretion of metabolite, norfenfluramine.
k_{mm} the rate constant for the formation of secondary metabolites from the primary metabolite, norfenfluramine.

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