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Metabolism of amylobarbitone in patients with chronic liver disease

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Summary

1. A single dose of amylobarbitone (3·23 mg/kg) was given by intravenous injection to each of ten healthy controls and two groups of five patients with chronic liver disease. A curve of serum amylobarbitone concentration against time was prepared for each subject and the proportion of the serum amylobarbitone bound to protein determined. The urinary excretion of the metabolite hydroxyamylobarbitone, ethyl (3 hydroxyisoamyl) barbituric acid was measured.

2. The degree of protein binding of serum amylobarbitone was reduced in the five patients (group I) with abnormally low concentrations of albumin in serum ($<$3·5 g/100 ml) but was normal in the five patients (group II) with normal serum albumin concentrations ($>$3·5 g/100 ml).

3. The equation for a double exponential decay was fitted to the concentration/time curves for amylobarbitone free in the serum water. The mean intercepts and rate constants were used to calculate the dimensions of mathematical models based on a two compartment open system.

4. The five patients (group I) who had abnormally low concentrations of albumin in serum showed impairment of amylobarbitone metabolism ; the rate constant $\beta(h^{-1})$ for the second exponential decay of serum amylobarbitone concentration was reduced ($P<0·01$), the urinary excretion of hydroxyamylobarbitone was reduced ($P<0·001$) and the mean serum water clearance (C_e ml/min) representing amylobarbitone elimination by metabolism was reduced.

5. The five patients (group II) who had normal concentrations of albumin in serum showed no impairment of amylobarbitone metabolism. Within the total patient group there were strong and significant positive correlations between the serum albumin concentration and each of the indices of the rate of amylobarbitone metabolism.

6. Both patient groups showed an increase in the first dispositional rate constant $\alpha(h^{-1})$ and in the clearance (C_t ml/min) representing transfer between central and peripheral compartments. The physiological basis for this observation is uncertain.

7. The clinical response to the single intravenous dose of amylobarbitone was not significantly greater ($P=0·11$) in the patient group (I) with slow amylobarbitone metabolism than in the patient group (II) with a normal rate of amylobarbitone metabolism.

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Introduction

The liver is the main site of barbiturate metabolism. The evidence for this assertion has been reviewed by several authors (Raventos, 1954 ; Mark, 1963 ; Bush & Sanders, 1967). More accurate localization of barbiturate metabolism to the liver microsomes was achieved by Brodie, Axelrod, Cooper, Gaudette, La Du, Mitoma & Udenfriend (1955). Fouts (1961) showed that the smooth surfaced microsomal fraction was responsible. Animal experiments have demonstrated impaired metabolism of several barbiturates after various forms of liver damage. Carbon tetrachloride administration (Kato, Chiesara & Vassanelli, 1962), partial hepatectomy (Masson & Beland, 1945), obstructive jaundice (McLuen & Fouts, 1961) and viral hepatitis (Kato, Nakamura & Chiesara, 1963) all reduce barbiturate metabolism in laboratory studies.

Several groups of clinical investigators have demonstrated impairment of oxidative drug metabolism in patients with chronic liver disease ; examples include the hydroxylation of tolbutamide (Ueda, Sakurai, Ota, Nakajima, Kamii & Maezawa, 1963), phenylbutazone (Levi, Sherlock & Walker, 1968), and glutethimide (Schmid, Cornu, Imhof & Keberle, 1964).

Investigation of the metabolism of barbiturates in patients with chronic liver disease has been hindered by the relative insensitivity of the standard assay methods. Mousel & Lundy (1940) described a single case of prolonged thiopentone anaesthesia in a patient with hepatic cirrhosis. Nine years later the first controlled study demonstrated a significantly increased duration of thiopentone effect in patients with liver disease (Shideman, Kelly, Lee, Lowell & Adams, 1949), and Dundee (1952) reported similar observations. The decay of serum pentobarbitone concentration during the first hour after intravenous administration was not slowed in patients with advanced liver disease (Sessions, Minkel, Bullard & Ingelfinger, 1954).

Amylobarbitone provides a suitable substrate for the study of barbiturate oxidation in man. The major metabolite, hydroxyamylobarbitone (ethyl (3 hydroxyisoamyl) barbituric acid) is excreted in the urine (Maynert, 1965) but the urinary excretion of unchanged amylobarbitone after hypnotic doses is negligible (Kamm & van Loon, 1966). The metabolism of hypnotic doses of amylobarbitone in healthy men and women has been investigated recently using a sensitive assay method based on gas-liquid chromatography (Balasubramaniam, Lucas, Mawer & Simons, 1970).

Although increased sensitivity to the central nervous system effects of morphine has been conclusively demonstrated in certain patients with liver disease (Laidlaw, Read & Sherlock, 1961) the position of barbiturates in this respect is undecided. Sessions *et al.* (1954) reported that patients with chronic liver disease were no more affected by pentobarbitone than were healthy control subjects. These findings were, however, contrary to those reported for thiopentone by Shideman *et al.* (1949) and Dundee (1952).

The investigation reported in this paper was designed to measure the rate of metabolism of amylobarbitone in patients with chronic liver disease. A preliminary report has already been published (Mawer, Miller & Turnberg, 1970).

Methods

Subjects

The ten patients were all suffering from chronic liver disease. The diagnosis was based on clinical and biochemical evidence and confirmed in eight cases by liver

biopsy (Table 1). At the time of investigation each patient was living outside hospital and the liver disease appeared to be in a steady state. None of the patients presented any of the signs or symptoms of hepatic precoma. Patient 1 suffered from concurrent chronic renal disease (blood urea 80 mg/100 ml); the low serum albumin concentration and the reduced excretion of hydroxyamylobarbitone could not be attributed solely to liver disease. In order to avoid distortion of the grouped results, data from this patient were excluded from several calculations. Patient 8 was studied both before and after surgical end-to-side portacaval anastomosis.

The patients were compared with ten healthy control subjects (four male and six female) whose ages ranged from 20 to 43 years (mean 29 years) and whose weights ranged from 53 to 85 kg (mean 63 kg).

The purpose and nature of the investigations were fully explained to all subjects and each gave informed consent.

Clinical procedures

Each patient was admitted to a short stay clinical investigation unit for up to 48 hours. A detailed drug history was taken and a full physical examination was made. Amylobarbitone (Sodium Amytal, Eli Lilly and Co. Ltd.) was administered at the dose of 3·23 mg/kg body weight by intravenous injection over a period of 3 minutes. Venous blood samples were taken at the time intervals after the start of the injection specified in Table 2. Blood samples were not taken from the arm that had received the injection. At the time of the first few injections an anaesthetist was present but this proved to be an unnecessary precaution.

All urine passed during the following 48 h was collected as two successive 24 h volumes.

The clinical effect in each patient was assessed by examining for signs of (a) lateral nystagmus, (b) impaired co-ordination and (c) altered level of consciousness, at 0·1, 0·5, 1·0, 2, 4, 12 and 24 h after injection. Each sign was scored from 0 (absent) to 4 (gross) on each occasion. The total score was thus a function of both the intensity and the duration of the drug effects. The method was similar to that adopted by Sessions *et al.* (1954) when studying the effects of pentobarbitone.

During the period in the investigation unit, venous blood was taken for the estimation of the following serum components: albumin (normal range 3·5–5·5 g/100 ml: Northam & Widdowson, 1967), globulin, bilirubin, alkaline phosphatase, glutamate-oxaloacetate transaminase and glutamate-pyruvate transaminase. Bromsulphthalein (5 mg/kg) was administered by intravenous injection. The serum concentration 45 min after injection was expressed as a percentage of the concentration at 5 min and termed the bromsulphthalein retention (Varley, 1962).

Laboratory procedure

The concentrations of amylobarbitone in serum were measured as described previously (Balasubramaniam, Mawer & Rodgers, 1969; Balasubramaniam *et al.*, 1970). A known amount of an internal marker, quinalbarbitone, was added to a measured volume of serum. The serum was acidified, saturated with ammonium sulphate and extracted with diethyl ether. The ether extract was concentrated and purified by two stage thin-layer chromatography on silica gel. The purified barbiturates were extracted from the gel into acetone, and concentrated. The relative

concentrations of amylobarbitone and internal marker in the purified extract were then measured by gas-liquid chromatography.

With minor modifications the same method was used to measure concentrations of hydroxyamylobarbitone in aliquots of the 24 h urine collections (Balasubramaniam, *et al.*, 1969). Pooled samples of serum from each patient were used to determine the degree of protein binding of amylobarbitone. The concentration of amylobarbitone in each serum pool was determined and aliquots from each were subjected to ultrafiltration, using the method of Walker (1967). The concentration of amylobarbitone in the ultrafiltrate was measured and the proportion of the serum amylobarbitone which was protein bound was calculated. Insufficient serum was available from patients 4 and 7 (Table 2) and estimates of the proportion of amylobarbitone protein bound were obtained from a curve relating observed values for the proportion to the concentration of serum albumin.

Concentration/time curves for amylobarbitone free in the serum water were obtained by multiplying the serum concentrations by the proportion of amylobarbitone in the free state. It has been shown that the proportion of the serum amylobarbitone which is bound to protein is independent of the amylobarbitone concentration over the range of amylobarbitone concentrations encountered in these experiments.

Fitting of concentration/time curves

Serum water amylobarbitone concentration/time curves were fitted by the equation for a double exponential function (Riggs, 1963).

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C (μg/ml) represents the serum water concentration at time t(h), A (μg/ml) the ordinate intercept of the first exponential function, B (μg/ml) the intercept of the second exponential function, and α and β (h^{-1}) the corresponding rate constants.

The dimensions of a hypothetical two-compartment model were calculated by substituting the mean values for A, B (μg/ml water), α and β (h^{-1}) into the equations of Riegelman, Loo & Rowland (1968). The applicability of the two-compartment model to amylobarbitone disposition in healthy subjects has already been demonstrated (Balasubramaniam *et al.*, 1970). The serum water clearance of amylobarbitone representing elimination from the central compartment (C_e ml/min) and that representing transfer between the central and peripheral compartments (C_t ml/min) were calculated from the following expressions:

$$\text{(a)} \qquad C_e = \frac{k_{el} \cdot V_1}{60} \text{ ml/min}$$

$$\text{(b)} \qquad C_t = \frac{k_{12} \cdot V_1}{60} = \frac{k_{21} \cdot V_2}{60} \text{ ml/min}$$

where V_1 and V_2 (ml) are the water equivalent volumes of the central and peripheral compartments, k_{el} (h^{-1}) is the first order rate constant for elimination, and k_{12} and k_{21} (h^{-1}) are the first order rate constants for transfer between the compartments.

Results

In Tables 1 and 2 the patients are arranged in ascending order of serum albumin concentration. Patients 1–5 (group I) had abnormally low concentrations of albumin

TABLE 1. *Clinical and biochemical features of patients with chronic liver disease*

Patient	Age (yrs)	Weight (kg)	Sex	Pathological features	Liver biopsy	Drug therapy	Serum albumin (g/100 ml)	Bromsulphthalein retention (% at 45 min)	Serum globulin (g/100 ml)	Serum bilirubin (mg/100 ml)	Serum alkaline phosphatase (K.A. units /100 ml)	Serum glutamate-pyruvate transaminase (units/100 ml)
1	22	84	F	Juvenile hepatic cirrhosis, portacaval shunt, oedema, ascites	Yes	Frusemide prednisolone spironolactone	1·0	—	2·2	0·4	13·5	20
2	56	72	M	Alcoholic cirrhosis, portacaval shunt	Yes	None	3·0	46	3·5	2·7	19·0	13
3	55	65	F	Chronic active hepatitis	No	Prednisolone	3·1	36	7·0	0·7	11·0	45
4	42	59	F	Portal cirrhosis, portal hypertension	No	Isoniazid rifampicin ethambutol	3·3	47	3·6	1·4	17·0	86
5	43	38	F	Primary biliary cirrhosis	Yes	None	3·3	39	6·4	2·6	150·0	54
6	33	70	M	Portal cirrhosis	Yes	None	4·0	48	3·8	1·9	6·9	130
7	29	50	F	Chronic active hepatitis	Yes	Lincomycin tetracycline	4·2	8	6·2	0·8	12·5	32
8a	21	70	M	Congenital hepatic fibrosis	Yes	None	4·4	13	2·8	0·5	10·5	
8b	21	62	M	As above 2 weeks after portacaval shunt		Phenobarbitone pentazocine	3·7	11	3·2	0·3	11·0	
9	51	76	M	Portal cirrhosis	Yes	Methaqualone diphenhydramine	4·8	7	2·2	0·5	8·5	24
10	25	77	M	Benign recurrent cholestasis, remission	Yes	None	5·0	6	2·1	0·7	19·0	9

TABLE 2. *Serum amylobarbitone concentrations, the degree of protein binding and the urinary excretion of hydroxyamylobarbitone after the intravenous administration of amylobarbitone* (3·23 *mg/kg*) *to patients with chronic liver disease*

	Serum amylobarbitone concentration (μg/ml)										Hydroxyamylobarbitone excreted (% of dose)	
Patient	0·1 h	0·5 h	1·0 h	4·0 h	12 h	24 h	30 h	36 h	48 h	Proportion protein bound	0–24 h	0–48 h
1				2·19	2·01	1·75	1·54			0·14	0·5	0·7
2	4·82	2·53	2·21	1·98	1·65	1·42	1·29		0·86 (60 h)	0·27	1·2	2·7
3	3·80 (0·2 h)	2·49	2·12	2·00	1·76	1·44	1·33			0·37	2·3	
4	7·14	4·64	3·82	2·76	2·35	1·76	1·65			(0·42)*	4·5	9·0
5	4·05	3·27	2·82	2·26	1·53	1·00	0·75		0·35	0·46	11·1	18·4
6	6·39	3·25	2·91	2·81	2·32			1·27	0·74	0·56	14·0	30·5
7	6·10	3·34	2·91	2·44	1·42	0·67	0·52			(0·54)*	15·2	
8a	6·15	4·40	3·69	2·89	2·01			0·84	0·50	0·59	11·4	19·4
8b	7·96	3·84	2·61	2·30	1·58			0·56	0·38	0·45	17·5	31·3
9	8·46	5·02	3·46	2·38		1·19	0·94		0·51	0·64	12·7	22·9
10	8·02	4·01	3·00	2·62	1·80	1·16	0·85		0·41	0·63	25·9	35·5
controls	7·54	5·67	4·51	2·64	2·10	1·37		0·96	0·62	0·61	17·3	34·0
±S.D.	0·76	0·93	0·68	0·32	0·41	0·29		0·17	0·13	0·05	3·6	5·5

(* Estimated from serum albumin concentration.)

TABLE 3. *Decay of amylobarbitone concentration in serum water after intravenous administration (3·23 mg/kg) to control subjects and to two groups of patients with chronic liver disease*

	Patient group I				Patient group II				Control group	
	Mean ± S.E.	*n*	*t*	*P*	Mean ± S.E.	*n*	*t*	*P*	Mean ± S.E.	*n*
Initial concentration										
A+B μg/ml	3·63 ±0·46	4	0·81	>0·40	3·80 ±0·45	5	1·15	>0·20	3·18 ±0·10	10
1st exponential decay										
Intercept A μg/ml	2·14 ±0·43	4	0·60	>0·50	2·55 ±0·44	5	1·69	>0·10	1·93 ±0·15	10
Rate constant αh^{-1}	2·77 ±0·75*	4	2·38	<0·05	4·55 ±1·48*	5	2·96	<0·02	1·47 ±0·20	10
Half time $T\frac{1}{2}$ h	0·30 ±0·06*	4	2·30	<0·05	0·22 ±0·06*	5	3·37	<0·01	0·54 ±0·06	10
2nd exponential decay										
Intercept B μg/ml	1·59 ±0·12	5	0·69	>0·50	1·25 ±0·08	5	0·01	>0·99	1·24 ±0·09	10
Rate constant βh^{-1}	0·021±0·003*	5	3·48	<0·01	0·041±0·005	5	1·67	>0·10	0·034±0·002	10
Half time $T\frac{1}{2}$ h	39·40 ±6·60*	5	3·80	<0·01	17·74 ±1·84	5	1·52	>0·10	21·10 ±1·23	10

Group I, serum albumin less than 3·5 g/100 ml. Group II, serum albumin greater than 3·5 g/100 ml. * Mean patient values which differ significantly from the corresponding control values.

in serum (<3·5 g/100 ml). Patients 6–10 (group II) had normal concentrations of serum albumin (>3·5 g/100 ml).

The proportion of the serum amylobarbitone bound to protein was reduced (Table 2) in patient group I (31·0 ± 6·9 ; % ± S.E.M., $n=4$) by comparison with the proportion in patient group II (60·5 ± 1·2, $n=4$; $t=4{\cdot}15$, $P<0{\cdot}005$) which was indistinguishable from control values (60·7 ± 1·6, $n=11$).

The concentrations of amylobarbitone in serum at intervals after the intravenous injection of amylobarbitone are given in Table 2. The concentration/time curves for different patients are not directly comparable because the relative proportions of bound amylobarbitone and free amylobarbitone differ markedly between patients.

Concentration/time curves for amylobarbitone free in the serum water were analysed as double exponential decay curves. The ordinate intercepts, rate constants and half times corresponding with the two exponential components are shown in Table 3.

The patients (group I) who had abnormally low concentrations of albumin in serum had a low mean rate constant β (h^{-1}) for the second exponential decay (Table 3). The same group excreted a reduced proportion of the dose as urinary hydroxyamylobarbitone (Table 2) during the first 24 h (4·8 ± 2·2, % ± S.E.M., $n=4$; control group 17·3 ± 1·1, $n=10$; $t=5{\cdot}53$, $P<0{\cdot}001$). Patient 1 was excluded from this calculation because renal disease may have contributed to the low excretion of hydroxyamylobarbitone in her case.

The patients (group II) who had normal concentrations of albumin in serum had normal values for β (h^{-1}) (Table 3) and for the urinary excretion of hydroxyamylobarbitone (Table 2).

Both groups of patients showed a significant increase in the rate constant α (h^{-1}) for the first exponential decay (Table 3).

The clinical response to the intravenous dose of amylobarbitone in patient group I (mean score 23·0, range 15 to 40) was not significantly greater than the response in patient group II (mean score 16·2, range 12 to 23) (Mann-Whitney U=6, $n_1=n_2=5$, $P=0{\cdot}11$).

Discussion

The analysis of the data presented in Table 2 has been based on the assumption that the rates of metabolism and distribution of amylobarbitone are directly proportional to the concentration of amylobarbitone free in the serum water. It has been assumed that the amylobarbitone-serum albumin complex does not penetrate readily into cells and does not gain access to the microsomal oxidase system. Martin (1965) and Brodie (1965) have made the same assumptions. Brodie also suggested that the biological effect of a drug is closely dependent on its concentration in the serum water.

When comparing the kinetics of drug disposition in different subjects who have normal concentrations of albumin in serum it is not important to distinguish between the free drug concentration and the total drug concentration because the degree of protein binding shows little individual variation. The distinction becomes important however when comparing drug disposition in healthy subjects with disposition in patients who have low serum albumin concentrations ; the low protein concentration produces a predictable fall in the degree of protein binding (Goldstein, 1949). Distri-

bution volumes and clearance values representing transfer or elimination may then be expressed in terms of ml of serum only if protein binding is negligible or if it can be assumed that the drug-albumin complex and the free drug are both distributed, metabolized and excreted with equal facility.

Two compartment mathematical models have been fitted to the concentration/time curves for amylobarbitone in serum water (Table 4). In the (group I) patients with low concentrations of albumin in serum the mean elimination clearance (C_e ml water/min) was reduced to half the control value (Table 4). This is believed to represent a reduction in the capacity of the liver for the oxidative metabolism of amylobarbitone. In the (group II) patients with normal concentrations of albumin in serum there was no reduction in the mean elimination clearance.

The reduced protein binding of amylobarbitone in the patients of group I was considered to be a direct consequence of the reduced concentration of albumin in serum. The reduced rate of amylobarbitone metabolism and the reduced concentration of albumin in serum were, however, considered to be parallel but independent consequences of reduced hepatic parenchymal cell function.

It is well known that the administration of drugs with the capacity to induce microsomal oxidase can increase the rate of elimination of other drugs. Levi *et al.* (1968) obtained shorter serum half times for phenylbutazone in those patients with chronic liver disease who were receiving known inducing agents. When selecting patients for the present study we were unable to find a sufficient number who were not receiving other drugs (Table 1). Thus it is likely that the indices of the rate of amylobarbitone metabolism in both patient groups were increased by the presence in each of two or three patients receiving other drugs. This effect did not, however, mask the slow metabolism of amylobarbitone in the patients with low concentrations of albumin in serum.

The serum albumin concentration in a patient with chronic liver disease may provide a useful guide to the capacity for oxidative drug metabolism. In this series of patients there was a strong positive correlation between the concentration of serum albumin and each of the following indices of the rate of amylobarbitone metabolism: (a) the rate constant for the second exponential decay β (h^{-1}), $r=0{\cdot}72$, $n=9$, $P<0{\cdot}05$; (b) the urinary hydroxyamylobarbitone excretion (% of dose during first 24 h), $r=0{\cdot}82$, $n=9$, $P<0{\cdot}01$; (c) the elimination clearance (C_e ml water/min),

TABLE 4. *Dimensions of the two compartment models which fit the serum water concentration/time curves for amylobarbitone in control subjects and in two groups of patients with chronic liver disease*

	Patient group I mean±S.E.	*n*	Patient group II mean±S.E.	*n*	Control group mean±S.E.	*n*
Body weight (kg)	63·6	5	68·6	5	62·6	10
Dose (mg)	205	5	222	5	202	10
Distribution volumes						
V_1 ml	54,900± 2,600	4	61,300± 7,300	5	64,300± 4,000	10
V_2 ml	79,500±17,900	4	114,000±19,400	5	91,300±10,200	10
Clearances						
Transfer C_t ml/min	1,580±550	4	2,640±730	5	840±100	10
Elimination C_e ml/min	41·0±5·1	5*	118·9±12·5	5	92·0±7·0	10

* C_e in patient 1 was calculated assuming A/α to be negligible. This introduces a 1% overestimation. Group I, serum albumin less than 3·5 g/100 ml. Group II, serum albumin greater than 3·5 g/100 ml.

$r=0{\cdot}99$, $n=7$, $P<0{\cdot}001$. Patient 1 was excluded from correlations a, b and c because the low serum albumin was partly due to renal disease. Patients 4 and 7 were excluded from correlation c because the serum albumin concentration had been used in the estimation of the proportion of amylobarbitone protein bound and thus indirectly in the derivation of C_e (ml/min). Levi *et al.* (1968) also found a significant correlation between the concentration of serum albumin and the serum half time of phenylbutazone in patients with chronic liver disease.

The degree of bromsulphthalein retention also correlated with the same indices of the rate of amylobarbitone metabolism (a) β (h^{-1}), $r=-0{\cdot}79$, $n=9$, $P<0{\cdot}02$; (b) urinary hydroxyamylobarbitone (% per 24 h), $r=-0{\cdot}65$, $P<0{\cdot}05$; (c) C_e (ml/min), $r=-0{\cdot}90$, $n=9$, $P<0{\cdot}005$. The other serum estimations which are used as clinical measures of hepatic function correlated poorly with the indices of amylobarbitone metabolism. The experience of Levi *et al.* (1968) with phenylbutazone was similar.

Both patient groups showed an increase in the first dispositional rate constant α (h^{-1}). Sessions *et al.* (1954) also found a more rapid decay of serum pentobarbitone concentration in patients with liver disease during the first 30 min after the administration of 120–180 mg by intravenous infusion. The physiological explanation for this phenomenon is not known but it may possibly be due to the general and regional circulatory changes which accompany chronic hepatic cirrhosis (Kontos, Shapiro, Mauck & Patterson, 1964).

The distribution volumes expressed as ml of serum water (Table 4) were comparable in all three groups as would be expected from the lack of significant differences between the values for the intercept concentrations A and B (μg/ml water) (Table 3).

Two of the patients who showed impairment of amylobarbitone metabolism had previously been subjected to surgical portacaval anastomosis as treatment for portal hypertension. It seemed possible that the reduced rate of amylobarbitone metabolism in these patients was due to the reduced total liver blood flow; surgical portacaval anastomosis produces a significant reduction in total liver blood flow (Redeker, Geller & Reynolds, 1958). The opportunity to study a patient (8) both before and after end-to-side portacaval anastomosis was therefore taken. Comparison of the data from experiment 8b with that from 8a (Table 2) shows no evidence of impairment of amylobarbitone metabolism attributable to the establishment of a surgical portacaval shunt in this patient.

The patient group (I) with slower metabolism of amylobarbitone did not show a significantly greater clinical response to the single intravenous dose than the patient group (II) with normal metabolism. This result is consistent with the observations of Sessions *et al.* (1954) who found no increase in the clinical response to intravenous pentobarbitone in patients with liver disease. It is consistent also with the measurements of amylobarbitone concentration free in the serum water which were not significantly greater in patient group I than in patient group II at 0·1 h ($P>0{\cdot}60$), 0·5 h ($P>0{\cdot}10$) or 1·0 h ($P>0{\cdot}05$). The influence of slower metabolism on the concentration (C) of amylobarbitone in serum water was first apparent at 4 h: patient group I, $C=1{\cdot}48\pm0{\cdot}12$ μg/ml $\pm$S.E.M., patient group II $C=1{\cdot}07\pm0{\cdot}07$, $t=2{\cdot}92$, $P<0{\cdot}02$ (control group $C=1{\cdot}04\pm0{\cdot}04$). The clinical effects of the intravenous dose were most obvious during the first hour or two and by 4 h it was difficult to detect signs of central nervous system depression.

In conclusion, it has been observed that a group of five patients with chronic liver disease and low concentrations of albumin in serum showed reduced binding of amylobarbitone to serum proteins and a reduced rate of oxidative metabolism of amylobarbitone. Neither of these abnormalities was detected in a group of five patients with chronic liver disease who had normal concentrations of albumin in serum. The initial rapid decay of serum amylobarbitone concentration after an intravenous dose was similar in both groups of patients. It is probably for this reason that the clinical response to the single intravenous dose of amylobarbitone was not significantly greater in the group of patients with the slower rate of amylobarbitone metabolism.

The concentrations of serum albumin and bromsulphthalein and the other serum components of diagnostic significance in chronic liver disease were measured in the Clinical Biochemistry Laboratory of Manchester Royal Infirmary under the supervision of Dr. A. H. Gowenlock. Dr. N. E. Miller was in receipt of a Clinical Pharmacology Research Scholarship from the Wellcome Foundation.

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