intravenously). This result was highly significant ($P<0.005$). This reduction in amplitude resulted from depression of the fusimotor system, for the H reflex was unaffected by this dose of thymoxamine. Methylamphetamine (0·2 mg/kg intravenously) increased the tendon jerks by 64% ($P<0.025$) without affecting the H reflex. An attempt is being made to block the effect of methylamphetamine with thymoxamine.

We would like to thank the Mental Health Research Fund for an equipment grant.

A. R. and D. G. S. were supported by Fellowships from the Wellcome Trust.

† Present address: Department of Pharmacology, Vanderbilt University, Nashville, Tennessee, U.S.A.

REFERENCES

BIRMINGHAM, A. T., AKUBUE, P. I. & SZOLCSANYI, J. (1967). A quantitative analysis of the antagonism of intravenous noradrenaline by thymoxamine or phentolamine on the blood pressure of a conscious cat. *J. Pharm. Pharmac.*, **19**, 137–145.

DAHLSTRÖM, A. & FUXE, K. (1965). Experimentally induced changes in the intraneuronal amine levels of bulbospinal neurone systems. *Acta physiol. scand.*, **64**, suppl. 247, 5–36.

ELLAWAY, P. H. & PASCOE, J. E. (1968). Noradrenaline as a transmitter in the spinal cord. *J. Physiol., Lond.*, **197**, 10*P*.

MATTHEWS, W. B. (1970). The clinical implications of the H reflex and of other electrically induced reflexes. In *Modern Trend in Neurology*, vol. 5, pp. 241–253, ed. Williams, Denis. London: Butterworths.

## The influence of dose on the distribution and elimination of amylobarbitone in healthy subjects

K. BALASUBRAMANIAM, G. E. MAWER* and P. J. SIMONS, *Departments of Medicine and Pharmacology, University of Manchester, Manchester* 13

The mean plasma amylobarbitone clearance rate $C_a$ (ml/min) in four healthy subjects did not change despite a twofold increase in the administered dose of amylobarbitone. Renal excretion of unchanged amylobarbitone was negligible and the plasma amylobarbitone clearance was mainly attributed to oxidation in the liver.

The elimination rate constant, $k_{el}$ $(\frac{1}{\text{time}})$, was recommended as a measure of elimination rate by Riegelman, Loo & Rowland (1968) but the $k_{el}$ for amylobarbitone has proved to be a dose dependent function, not a stable individual characteristic.

Serum amylobarbitone decay curves were determined on three separate occasions in each subject after intravenous doses of 3·23, 4·84 and 6·46 mg/kg. The collection and analysis of samples and the fitting of a two compartment model to the double exponential decay curves have been described earlier (Balasubramaniam, Lucas, Mawer & Simons, 1970).

TABLE 1. *Influence of dose on amylobarbitone disposition*

| | Distribution volumes | | Transfer | Elimination | | |
|---|---|---|---|---|---|---|
| | Initial Distribution | Steady State | Clearance rate | Clearance rate | Rate Constant | Decay Half-time (slow-phase) |
| Dose mg/kg | $V_1$ (ml) | $V_{dss}$ (ml) | $C_t$ (ml/min) | $C_a$ (ml/min) | $k_{el}$ (1/h) | $T_{\frac{1}{2}}$ (h) |
| 3·23 | 27,500 | 68,000 | 320 | 37·4 | 0·082 | 21·6 |
| | ± 800 | ±5,500 | ±40 | ±2·9 | ±0·006 | ±2·0 |
| 4·84 | 42,200 | 76,700 | 480 | 39·8 | 0·057 | 22·0 |
| | ±1,800 | ±8,400 | ±60 | ±2·5 | ±0·003 | ±0·7 |
| 6·46 | 39,100 | 81,600 | 520 | 37·8 | 0·058 | 25·7 |
| | ±2,000 | ±6,700 | ±60 | ±2·8 | ±0·003 | ±1·0 |

Mean values ± S.E.M. ($n$=4). Mean body weight 66 kg (range 61–70 kg).

The first increment in dose caused a large increase ($P<0{\cdot}001$) in the initial distribution volume $V_1$ and in the rate of transfer $C_t$ (ml/min) between the two compartments ($P<0{\cdot}10$). The increase in $V_1$ has been reproduced without increase in dose in subjects performing physical exercise or sucking glyceryltrinitrate tablets; it is attributed to peripheral vasodilatation. The increase in $V_1$ caused a reciprocal fall in $k_{el}$ but there was no change in amylobarbitone elimination expressed as the plasma clearance rate $C_a$.

The second increment in dose caused no significant change in $V_1$, $C_t$, $C_a$ or $k_{el}$.

REFERENCES

BALASUBRAMANIAM, K., LUCAS, S. B., MAWER, G. E. & SIMONS, P. J. (1970). The kinetics of amylobarbitone metabolism in healthy men and women. *Br. J. Pharmac.*, **39**, 564–572.

RIEGELMAN, S., LOO, J. C. J. & ROWLAND, M. (1968). Shortcomings in pharmacokinetic analysis by conceiving the body to exhibit the properties of a single compartment. *J. Pharm. Sci.*, **57**, 117–123.

## Preliminary observations on the elimination of amylobarbitone by patients with chronic liver disease

G. W. MAWER, N. E. MILLER* and L. A. TURNBERG, *Department of Pharmacology, University of Manchester, and Division of Gastroenterology, Royal Infirmary Manchester* 13

Amylobarbitone (3·23 mg/kg) was given by intravenous injection over a 3 min period without loss of consciousness to seven patients with chronic liver disease. The serum amylobarbitone decay curves were determined and each was fitted by a two compartment mathematical model. The results were expressed as the half-time $T\frac{1}{2}$ (h) for the slow decay of serum amylobarbitone concentration, the plasma amylobarbitone clearance $C_a$ (ml/min) and the steady state distribution volume $V_{dss}$ (ml). Bromsulph alein retention and other conventional indices of liver function were measured. The purpose and nature of the experiments were fully explained and each patient, gave informed consent.

TABLE 1. *Amylobarbitone elimination and bromsulphalein (BSP) retention in patients with chronic liver disease*

| Description of patient and long term drug therapy | Distribution volume ($V_{dss}$) (ml) | Plasma clearance rate ($C_a$) (ml/min) | Half time (slow phase) ($T\frac{1}{2}$) (h) | BSP retention (45 min) (%) | Age (years) | Weight (kg) |
|---|---|---|---|---|---|---|
| Juvenile hepatic fibrosis; portacaval anastomosis; frusemide, prednisolone, spironolactone | 111,000 | 26 | 49 | | 22 | 84 |
| Alcoholic cirrhosis; portacaval anastomosis; no drugs | 115,000 | 28 | 49 | 46 | 56 | 72 |
| Post-necrotic cirrhosis; no drugs | 69,000 | 36 | 22 | 48 | 33 | 70 |
| Primary biliary cirrhosis; no drugs | 46,000 | 33 | 17 | 39 | 43 | 38 |
| Portal cirrhosis; isoniazid, rifampicin, ethambutol | 43,000 | 22 | 23 | 47 | 42 | 59 |
| Portal cirrhosis; diphenhydramine, methaqualone | 83,000 | 53 | 20 | 7 | 51 | 76 |
| Active chronic hepatitis: lincomycin, tetracycline | 53,000 | 55 | 12 | 8 | 29 | 50 |
| Healthy controls; mean | 61,000 | 35 | 21 | <5 | 29 | 63 |
| No drugs (range) ($n=10$) | (36,000–84,000) | (23–51) | ±4 (S.D.) | | (20–43) | (53–85) |