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A method for studying spinal pharmacology in man

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Using human volunteers for pharmacological studies of spinal reflexes has two possible advantages over animal experiments: (*a*) the subject is conscious, co-operative and has an intact nervous system, and (*b*) the results of such studies are immediately relevant to therapy of spinal diseases. Techniques for studying the excitability of α- and γ-motoneurones in man have been described in detail (Matthews, 1970), but they have been little used for pharmacological work. Evidence from animal experiments suggests that bulbospinal noradrenergic pathways in the mammalian spinal cord (Dahlström & Fuxe, 1965) may be important in the regulation of fusimotor neurone discharge (Ellaway & Pascoe, 1968). In order to extend these observations to normal human volunteers a technique has been devised which measures the following:

1. The isometric tension of the gastrocnemius-soleus muscle produced reflexly by standard taps to the Achilles tendon, measured with a 10 kg strain gauge.

2. The maximum amplitude of the H reflex recorded from the muscle with skin electrodes by stimulating the Ia afferent fibres in the medial popliteal nerve. This reflex by-passes the muscle spindles and tests the excitability of the α-motoneurone pool (Matthews, 1970).

3. The isometric tension produced by a stimulus to the medial popliteal nerve at an intensity at which the H reflex is completely blocked by antidromic conduction in α-motor fibres. This procedure tests transmission at the neuromuscular junction.

4. The tension produced by a stimulus applied to the belly of the muscle through skin electrodes, thus testing the integrity of the contractile mechanism of the muscle.

These measures allow separation of central and peripheral effects of a drug. In addition, the action of a drug on fusimotor neurones can be distinguished from an action on α-motoneurones, for an alteration in the amplitude of the tendon jerk without a change in the H reflex suggests an action on the fusimotor system.

Preliminary results of two double-blind balanced randomized studies using a saline control in six male volunteers suggest that adrenergic mechanisms are concerned in the regulation of tendon jerk reflexes. Results were calculated as a percentage of the preinjection values, and the significance of the mean differences between drug and saline was tested. Thymoxamine, a specific α-adrenoceptor blocking drug (Birmingham, Akubue & Szolcsanyi, 1967) produced a marked reduction in the amplitude of the tendon jerk (mean difference= -66% with a dose of 0·1 mg/kg

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.

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

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

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