Br. J. Pharmac. Chemother. (1968), **33**, 117–128.

THE TIME COURSE OF BARBITURATE ACTION IN MAN INVESTIGATED BY MEASUREMENT OF SMOOTH TRACKING EYE MOVEMENT

BY

H. NORRIS*

From the Department of Pharmacology, University College London, Gower Street, London, W.C.1

(*Received November* 21, 1967)

The classification of barbiturates according to the duration of their actions (Sollman, 1957 ; Goodman & Gilman, 1965) is based on measurements of the duration of depression in laboratory animals. As regards human sleep, reputedly short, intermediate and long acting barbiturates have not been found to have distinguishable durations of effects (Lasagna, 1956 ; Hinton, 1961, 1963). Whether it is to be concluded that there is a species difference, such that in man the barbiturates all follow the same time course of action, is uncertain. As a step towards the resolution of such uncertainties, measurements have been made on an aspect of human behaviour which is sensitive to barbiturate action and is amenable to experimental control.

Eye movements are considerably affected by moderate doses of barbiturates. The small amplitude " barbiturate nystagmus " which appears on deviation of gaze in any direction is a well-known side effect. But the drugs also suppress opto-kinetic nystagmus (Bergman, Nathanson & Bender, 1952), smooth tracking movement (Rashbass, 1959) and convergence-divergence movement (Westheimer & Rashbass, 1961 ; Westheimer, 1963). Moderate doses, however, leave intact the very fast saccadic movement (Rashbass, 1961) and vestibular stimulated nystagmus (Rashbass & Russell, 1961).

Barbiturate suppression of opto-kinetic nystagmus was quantified by Rashbass & Russell (1961). In the present study suppression of the more stable smooth tracking movement is measured to compare the time course of action of three barbiturates.

METHODS

Measurement technique

Smooth tracking eye movement was elicited by asking the subject to follow a moving target with his eyes, keeping his head still. The target, a spot of light back-projected on to a translucent screen 57 cm from the eyes, oscillated with horizontal simple harmonic motion. The amplitude of the oscillation subtended 40° at the subject's eyes.

The technique of electro-oculography (reviewed by Shackel, 1967) was used to record eye movement. The potential difference between the cornea and the retina generates an electric field in the surrounding tissues. Electrodes are placed at the external canthi and the potential difference between them varies approximately linearly with the angle of horizontal conjugate eye movement. A d.c.

* Present address: Department of Pharmacology, London Hospital Medical College, Turner Street, London E.1.

amplifier and polygraph were used for recording. For calibration the subject performed a standard movement repeatedly while the amplifier gain was adjusted to produce a corresponding standard output.

The eyes reproduce the sinusoidal target movement as long as the smooth tracking response can match the angular velocity of the target (Fig. 1a). When this is suppressed, the consequent lag is compensated by step-like saccadic movements, with little change in the total amount of movement (Fig. 1b). To measure the amount of smooth tracking movement when it is interspersed with varying saccadic jerks an electronic analogue technique was used.

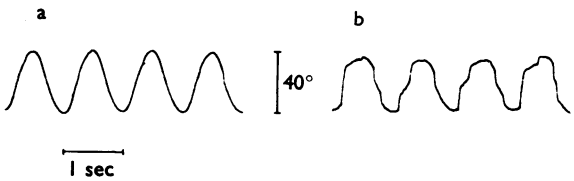

Fig. 1. Smooth tracking and saccadic eye movements. In (a) the smooth tracking response matches the target velocity almost throughout, so there are just a few small saccadic movements. In (b) the smooth tracking response is suppressed and the consequent lags are largely compensated by large and frequent saccadic jerks.

The principal operations performed by the circuits, which are based on Philbrick K2-w operational amplifiers, are outlined. The eye movement potential is differentiated to get a signal corresponding to the velocity of movement. This is rectified to get the absolute value of velocity. A gating circuit then takes out the spikes which represent the high velocity saccades leaving only the slower smooth component. This is integrated over the duration of each cycle of the target's oscillation to yield a signal whose final level corresponds to the amount of tracking movement in each cycle. The integrator output is written out and calibrated so that it represents the amount of smooth tracking per cycle as a percentage of the target movement.

Subjects and procedure

Eighteen undergraduate students of both sexes were used as subjects. To ensure adequately good eye movement measurement, preliminary tests were made of the signal-to-noise ratio in volunteers. About a quarter were rejected on this basis.

Subjects sat alone in a quiet, evenly illuminated room. They had half an hour of practice to stabilize their level of performance in the tracking task before their use in drug experiments. At the start of each drug measurement session subjects had a further 20 min practice during which an oscillation frequency was selected for each individual at which he could track 80% to 95% of the target movement. Frequencies of 0.7 to 1.2 c/s were used. Thus, in spite of differences in ability, subjects were made to perform at roughly the same level in terms of the percentage tracked.

To study the course of barbiturate action, observations of tracking were made every 8 min for 2 hr 40 min. Four of these were made at 28, 20, 12 and 4 min before the drug administration to establish the basal level. Seventeen observations were then made 4 min to 2 hr 12 min after drug administration. For each observation the average of a pair of measurements was taken. For each measurement the subject tracked about fifteen cycles of oscillation and the percentage tracked over the ten cycles following the initial three cycles was recorded and averaged. Such a pair of measurements occupied about 1 min and calibration checks preceded and followed each pair. Subjects generally read between observations and were not allowed to doze. With a placebo, performance remains close to the basal level. Typically there is an increase of about 5% of target movement tracked over 2 hr. With trained and co-operative subjects, substantial decreases from the basal level occur only as a consequence of drug action.

As an adjunct to the measurement of tracking suppression an attempt was made to record how the drugs affected the feelings of the subjects. A check list of feelings and sensations enlarged by

Steinberg from that used by Dickins, Lader & Steinberg (1965) was employed. In the 1 min before each tracking measurement the subject scanned through the thirty-six items, marking those which described his feelings at that moment.

Drug administration

Quinalbarbitone, pentobarbitone and phenobarbitone were studied, being common to the studies of Lasagna (1956) and Hinton (1963). The sodium salts were used. Each drug was given in two doses which were in the ratio of 3:5. The six preparations used were: quinalbarbitone sodium, 75 mg and 125 mg; pentobarbitone sodium, 75 mg and 125 mg; phenobarbitone sodium, 125 mg and 210 mg.

The drugs were given in identical gelatine capsules, and swallowed with about 100 ml. of water. A " double blind " administration was used, neither the subject nor the experimenter knowing which preparation was given.

Subjects were required to have had no solid food for 5 hr before taking the drugs. Tea and coffee were permitted in moderate amounts, alcohol was forbidden for the whole day.

Experimental design

Six preparations were compared. Because intersubject differences were large and subjects were available for no more than two sessions, an incomplete block design was used. A fully balanced incomplete block design for six preparations taken two at a time requires fifteen subjects. With a repetition in reverse order to balance first and second session administrations, thirty subjects would be needed. In order to economize in subjects, an unbalanced portion of the full design was used. The within-subject comparisons covered were between unlike doses of the same drug (three subjects), and between like doses of different drugs (six subjects). First and second administrations were balanced by a reversed order repetition, so eighteen subjects were used. The thirty-six records obtained comprised six for each dose of each drug. The first and second sessions were taken one week apart.

RESULTS

Tracking suppression data

The changes in percentage tracked from the pre-drug basal level were averaged over the six subjects who had each preparation. The averages are shown plotted against time in Fig. 2. Double exponentials of the form $Y = Ae^{-bt} - Ce^{-dt}$ are fitted to the averaged data. Drug effects might reasonably be expected to follow this type of function. Effects would build up exponentially as the drug is absorbed then decay exponentially as the drug passes out of circulation. The approximate fittings were made by taking $\log_{10} Y$ and fitting a straight line by the least squares method to the decay phase points. Differences between this line and $\log_{10} Y$ values over the build-up phase were then fitted to " peel off " the other term (Riggs, 1963). Small adjustments were made by inspection to improve the fit of the combined function to the original Y values. By the χ^2 test for goodness of fit all fittings are satisfactory, the poorest being that for quinalbarbitone 75 mg ($0.80 < P < 0.90$). Parameters for each curve are given below:

Pheno	125 mg	$Y = 63\ e^{-0.069t} - 34\ e^{-0.0097t}$
Pheno	210 mg	$Y = 78\ e^{-0.060t} - 46\ e^{-0.0051t}$
Quinal	75 mg	$Y = 661\ e^{-0.226t} - 63\ e^{-0.0159t}$
Quinal	125 mg	$Y = 309\ e^{-0.131t} - 74\ e^{-0.0101t}$
Pento	75 mg	$Y = 191\ e^{-0.099t} - 76\ e^{-0.0138t}$
Pento	125 mg	$Y = 479\ e^{-0.221t} - 58\ e^{-0.0039t}$

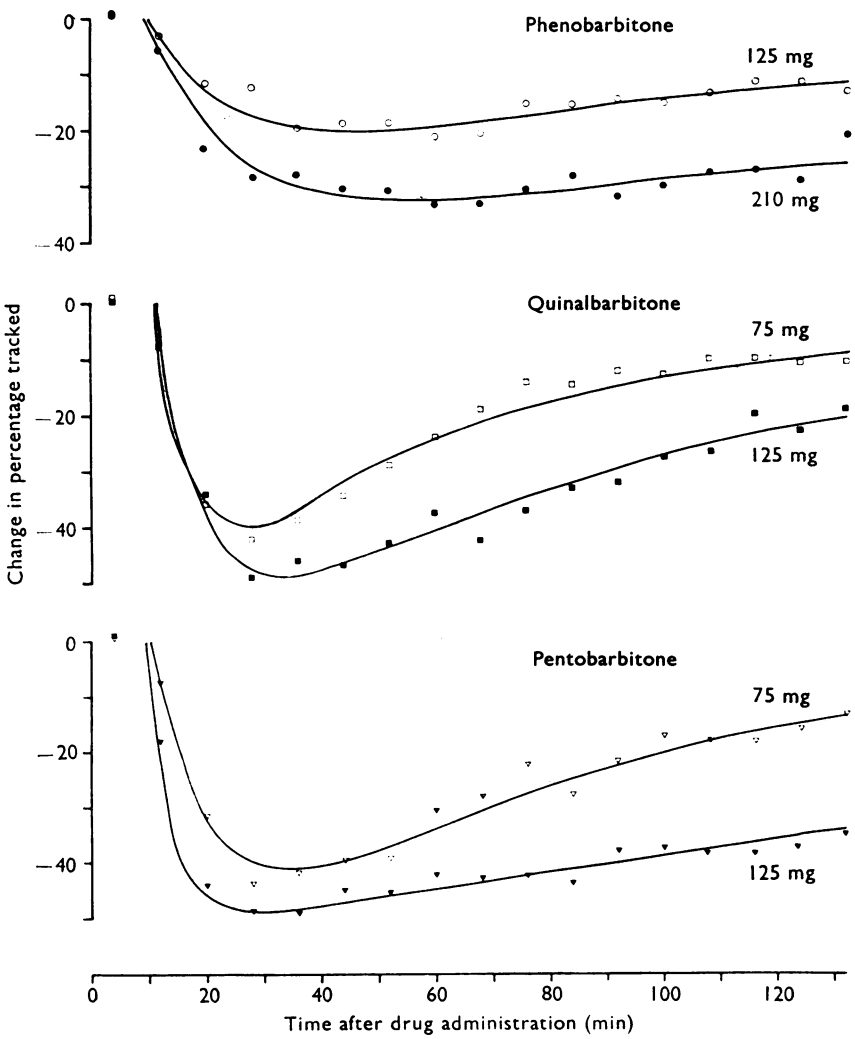

Fig. 2. Average tracking suppression is plotted against time for each drug preparation. At each post-drug observation the change in percentage tracked from the mean pre-drug level was determined. These have been averaged over the six subjects who had each preparation. Phenobarbitone (circles), quinalbarbitone (squares) and pentobarbitone (triangles) all show rapid deterioration in performance then gradual recovery, but the course taken differs between doses and between drugs. Exponentials of the form $Y=A\ e^{-bt}-C\ e^{-dt}$ were fitted to the averaged data and the parameters of each curve are given in the text.

Larger doses produce large effects which last longer. Quinalbarbitone and pentobarbitone are similar. The apparent differences between them are only of the order of differences between doses of either. Phenobarbitone seems to be qualitatively different. Its effects are less pronounced but more prolonged. However, these averaged data include subject as well as drug and dose differences.

As the design was not balanced familiar analysis of variance techniques are not applicable. Instead the method of least squares, on which analysis of variance techniques are based, was directly applied (Kendall & Stuart, 1961). Assuming the usual additive model, estimates were made of the effects attributable to each drug, dose and subject. A residual variance estimate with 13 degrees of freedom was obtained from the overall sum of squares minus the sum of squares attributable to drug, dosage and subject effects. The difference between first and second session administrations was not taken out because it was quite non-significant. From the dispersion matrix of drug and dose estimators, the appropriate variance estimate for each comparison between effects was obtained. The significance of differences was determined by Student's *t* test.

TABLE 1

(a) MEAN OVERALL TRACKING SUPPRESSION

Corrected estimates of the average decrease in the percentage tracked from 12 min to 2 hr 12 min after the drug administration. The table includes tests of the significance of dose-effect regressions and of the differences between drugs.

	Estimates of mean effect			Significance tests	
	75 mg	125 mg	210 mg	*t*	*P*
				(Dose regressions)	
Phenobarbitone	—	11	25	2·6	<0·05
Quinalbarbitone	23	40	—	3·2	<0·01
Pentobarbitone	22	34	—	2·5	<0·05
				(Drug differences)	
Phenobarbitone *cf.* quinalbarbitone	—	—	—	5·2	<0·001
Phenobarbitone *cf.* pentobarbitone	—	—	—	3·9	<0·01
Quinalbarbitone *cf.* pentobarbitone	—	—	—	1·3	N.S.

(b) POTENCY RATIOS OF MEAN OVERALL SUPPRESSION

Potency ratios and 0·05 fiducial limits of phenobarbitone compared with quinalbarbitone and pentobarbitone, together with the dose equivalents.

	Potency ratio	Dose equivalent (mg)	0·05 fiducial limits Ratio	Dose (mg)
Phenobarbitone:quinalbarbitone	1:2·7	210:79	1:2·3–3·3	210:63–93
Phenobarbitone:pentobarbitone	1:2·5	210:85	1:2·1–3·1	210:69–101

Table 1 presents the analysis of the mean overall tracking suppression, that is the average of all observations from 12 min to 2 hr 12 min after the drug administration. Table 1 (a) shows corrected estimates of the mean overall effect of each preparation, the effect of subject differences having been taken out. The comparisons between drugs show phenobarbitone to be significantly less effective even in these larger doses. As the dose-effect regressions are significant (and there are no significant deviations from parallelism) the data were treated as if from a parallel line bioassay, to estimate the potency ratios and fiducial limits (Finney, 1964). Table 1 (b) gives the ratios, showing phenobarbitone to be between 2 and 3 times less effective over the first 2 hr of its action. Figure 3 illustrates these dose-effect relationships.

Phenobarbitone at 210 mg has roughly the same overall effectiveness as quinalbarbitone and pentobarbitone at 75 mg. To see how different the time course of these effects is, the period was split into two and the tracking suppression over the first hour compared with that over the second. Corrected estimates of the differences between the mean tracking suppression over the first hour (12 min to 68 min) and over the second

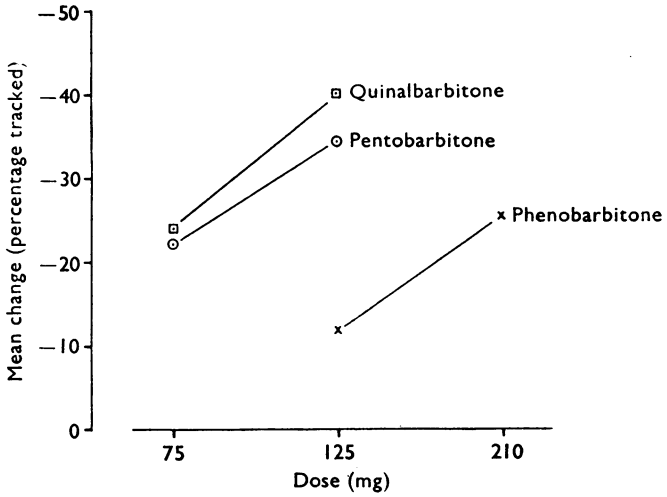

Fig. 3. Relationship of mean overall effect to dose for the three drugs. Corrected estimates of the mean tracking suppression over the period 12 min to 2 hr 12 min after the drug administration are plotted against dose, which is on a log scale. Treating the data as a parallel line bioassay the potency ratios show phenobarbitone 210 mg to be equivalent over this period to quinalbarbitone 79 mg and to pentobarbitone 85 mg.

hour (76 min to 132 min) were calculated. Phenobarbitone 210 mg is equally effective over the two periods with less than 1% decrease over the second hour. Quinalbarbitone 75 mg and pentobarbitone 75 mg both exert only half the tracking suppression over the second hour compared with the first. The percentage tracked increases by 21 and 14 respectively. The difference between phenobarbitone and the other drugs in this respect is significant ($P<0.02$).

The time courses are also compared in terms of the maximum amount of tracking suppression and the time at which it occurred. Table 2 (a) gives corrected estimates of the amount and the time of the peak effect for each preparation. Comparisons between drugs given in Table 2 (b) show that phentobarbitone exerts a significantly smaller peak effect and that it achieves it significantly later.

TABLE 2

(a) MAXIMUM TRACKING SUPPRESSION

The maximum amount of change in the percentage tracked and the time at which it occurred.

	Amount (% tracked)			Time (min)		
	75 mg	125 mg	210 mg	75 mg	125 mg	210 mg
Phenobarbitone	—	26	38	—	59	61
Quinalbarbitone	52	57	—	32	40	—
Pentobarbitone	43	48	—	40	27	—

(b) SIGNIFICANCE TESTS ON MAXIMUM SUPPRESSION

Comparisons between the drugs in terms of the amount and the time of the maximum tracking suppression.

		t	P
Phenobarbitone *cf.* quinalbarbitone	amount	5·6	<0·001
	time	3·7	<0·01
Phenobarbitone *cf.* pentobarbitone	amount	3·5	<0·01
	time	4·0	<0·01
Quinalbarbitone *cf.* pentobarbitone	amount	2·1	N.S.
	time	0·4	N.S.

It is concluded that there is no significant difference between quinalbarbitone and pentobarbitone. Phenobarbitone is by comparison 2 or 3 times less effective and has a significantly more prolonged time course over the period studied.

Subjective effects

The heterogenous items in the check list fell readily into three groups. Group A comprises the four items "absorbed, alert, clear-headed, efficient." These items were used frequently before the drug was given and less frequently thereafter. Group B comprises the nine items "confused, dizzy, dreamy, drowsy, find-it-difficult-to-concentrate, lethargic, mentally slow, muzzy, tired." These were applied infrequently before the drug and more frequently thereafter. The remaining twenty-three items were applied about equally frequently before and after drug administration so they convey little about subjective changes induced.

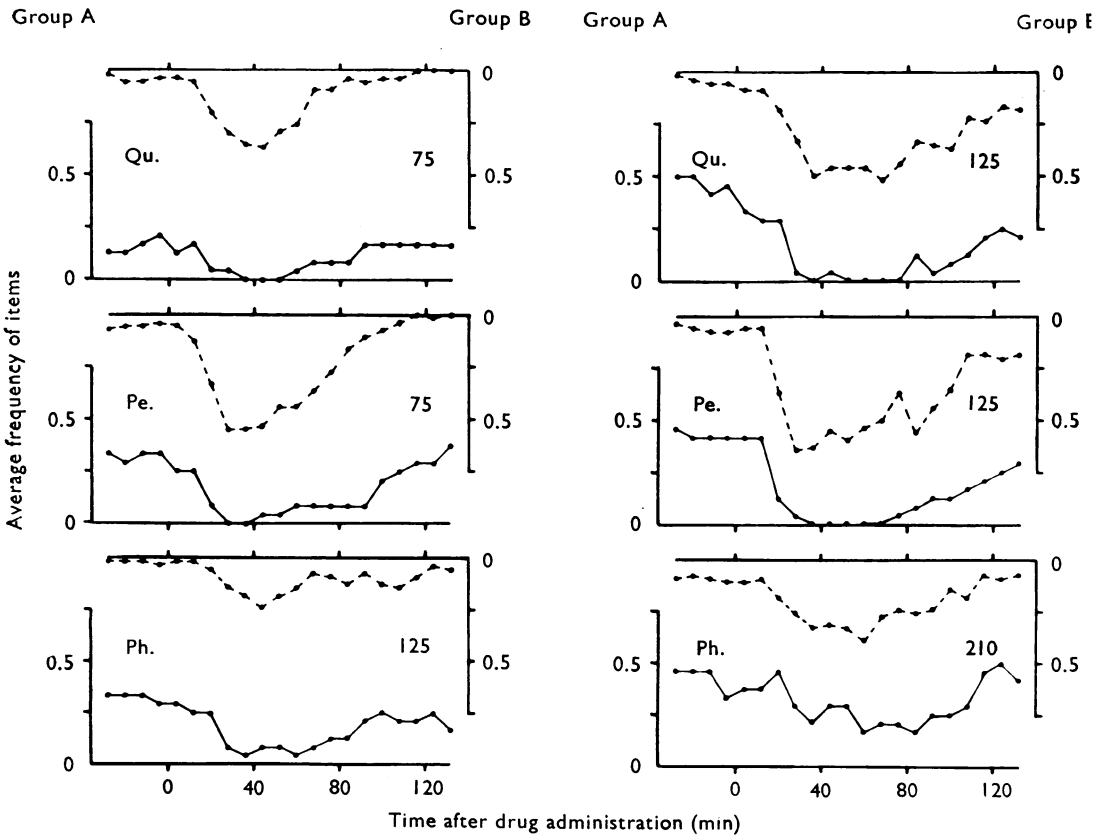

Fig. 4. Subjective changes for each drug preparation. The average frequency of application of the two groups of items is plotted against time for each preparation. Group A items (lower solid line) are plotted on the left-hand ordinate and group B items (upper dashed line) on the right-hand (inverted) ordinate. Group A comprises the items "absorbed, alert, clear-headed, efficient." Group B comprises "confused, dizzy, dreamy, drowsy, find-it-difficult-to-concentrate, lethargic, mentally slow, muzzy, tired."

The frequency of application was averaged over all the items in each group. Figure 4 shows the average frequency of group A and group B items against time, averaged over the six subjects who had each preparation. Some limitations of this type of data are evident. For example, the subjects who had quinalbarbitone 75 mg did not apparently feel particularly " absorbed, alert, clear-headed, or efficient " before taking the drug, so little of the drug-induced change could be conveyed by this group of items. But apart from this, group A and group B items show fair consistency in the course of changes induced by each preparation. Larger doses consistently produced larger effects which were more sustained. Quinalbarbitone and pentobarbitone were similar in producing marked subjective changes which declined quite swiftly towards the pre-drug level. Phenobarbitone showed less pronounced effects which were nevertheless more prolonged. Comparison of the subjective effects in Fig. 4 with the concurrently but independently measured eye movement effect in Fig. 3 shows the considerable similarity in time course of these different effects.

DISCUSSION

The conclusion that the effects of phenobarbitone are less pronounced but more prolonged than those of quinalbarbitone and pentobarbitone comes as no surprise. But as other studies found no difference in duration of action some factors which influence time course are discussed.

Absorption. Variability of effects following oral administration was noted in some of the earliest work on duration of action. Werner, Pratt & Tatum (1937) used oral administration in the rabbit but obtained useful data from intravenous and intraperitoneal administration only. With oral administration of shorter acting drugs, " . . . variations were of such a size that one must consider all barbiturates studied as having oral durations of the same order of magnitude."

Clinical usage is predominantly by oral administration, however, and a small study was made of the role of stomach contents in delaying absorption. Subjects had the same dose

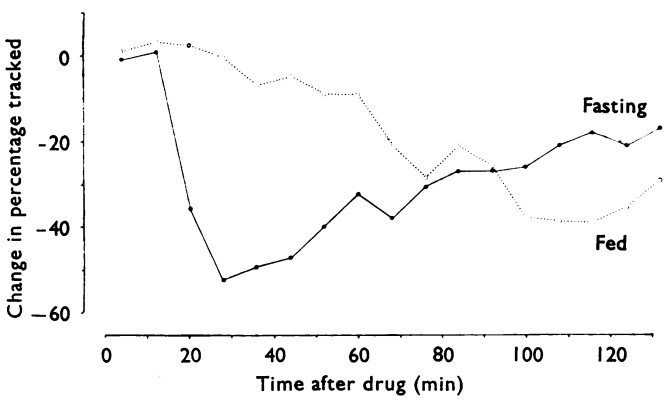

Fig. 5. Effect of a previous meal on the time course of quinalbarbitone effects. Tracking suppression is plotted against time for a subject who on two occasions had quinalbarbitone sodium 125 mg. The full line shows the course of effects when he had fasted for 10 hr (overnight). The dotted line shows the course of effects when a fatty and proteinous meal had been taken 3 hr before the drug.

of drug on two occasions. On one they had had no food for more than 10 hr (overnight) and on the other they had had breakfast 2 or 3 hr earlier. Figure 5 illustrates the degree of delay in effects produced in a subject whose meal taken 3 hr earlier was fatty and proteinous. Lighter meals produced lesser delays when 2 or 3 hr separated the meal from the drug administration. With 5 hr separation the effects were indistinguishable from those after 10 hr fasting, so 5 hr abstinence was imposed on all subjects in the study proper.

A wealth of work by Brodie, Schanker and their associates, recently summarized by Bush (1963), shows that the barbiturates pass readily through membranes in accordance with their degree of dissociation and lipid-water partition coefficients. Thus they are well absorbed from the stomach as from other parts of the alimentary canal. Hogben, Schanker, Tocco & Brodie (1957) have demonstrated this in man with quinalbarbitone in dilute solution. But being weakly acidic compounds, barbiturates are very sparingly soluble in acid gastric secretions. The presence of food will therefore delay absorption by delaying dissolution, both by stimulating acid secretion and by delaying the passage of drug particles into the less acid milieu of the intestine. Presumably proteinous foods cause longer delay than carbohydrates.

Elimination. It is generally assumed that the duration of action of all but the extremely lipid soluble and short acting barbiturates is determined principally by the processes of metabolism and excretion (Bush, 1963). But the rates of these processes in man are remarkably slow according to the estimates quoted by Mark (1963). For ease of comparison the exponential rates he quotes from diverse sources are expressed here in terms of half-life. For phenobarbitone this is about 3–6 days and for quinalbarbitone and pentobarbitone about 1 day. Yet the durations of the effects are usually thought of as a few hours. The half-life of tracking suppression, estimated from the exponentials fitted to the averaged data is also in terms of hours. Taking the more comparable doses, the half-life of phenobarbitone (210 mg) effect is about 3.5 hr and that of the others at 75 mg about 1 hr.

The plasma concentration of drug must decline as a function of redistribution within the body. Circulating drug will rapidly penetrate the highly vascular central nervous system but pass more slowly into the less vascular bulk of other tissues (Butler, 1963). As it does so, plasma concentration will decrease several-fold. Probably this process accounts for the initial and with moderate doses the greater part of the decrease in effects. The more prolonged time course of phenobarbitone would in that case be attributable primarily to its slower diffusion through membranes. Phenobarbitone has a lower lipid-water partition coefficient (Bush, 1963) and would therefore be expected to be absorbed and redistributed more slowly.

After the initial decline in effects attributable to redistribution of the drug, most of the dose will remain active, being slowly metabolized and excreted. Thus even the shorter acting drugs exert slight but discernible effects many hours after administration. In line with the findings of the present study, Latz & Kornetsky (1965) found that the effects of quinalbarbitone 200 mg declined quite rapidly right from their earliest measurements made 30–60 min after administration. But Kornetsky, Vates & Kessler (1959) found slight but statistically significant impairment on three psychomotor tests 14–15 hr after

quinolbarbitone 200 mg. Goodnow, Beecher, Brazier, Mosteller & Taguiri (1951) reported that after pentobarbitone 100 mg psychomotor impairment "was found to continue in a highly suggestive (qualitative trend) but not statistically significant degree . . . 14 hr after medication." Phenobarbitone is known to accumulate considerably from daily administrations (Butler, Mahaffee & Waddell, 1954) and on the evidence of the rates of metabolism quinalbarbitone and pentobarbitone must accumulate also. Tolerance in the form of increased metabolism and decreased sensitivity of the central nervous system are thought to develop fairly rapidly and to an important extent (Butler *et al.*, 1954; Maynert & Klingman, 1960; Goodman & Gilman, 1965).

Time courses in man. Studies were made of these particular barbiturates used as hypnotics in hospitalized patients by Lasagna (1954) and Hinton (1961). The more prolonged action of phenobarbitone, observed in numerous animal studies and now confirmed in man, was not found by either. But as patients were understandably not starved before retiring to bed and taking their sedatives, there would have been varying delays in absorption. Second, drugs were given each night so that accumulation would have occurred. Thus each dose would have contributed an increment to a varying pre-existing level rather than exerting a discrete effect. Third, these studies were concerned with barbiturates used as hypnotics, that is to promote normal nightly sleep in man. Such sleep has its own temporal characteristics and may not necessarily be closely related to the persistence of the drug in the body.

Besser & Duncan (1967) have recently investigated the time course of phenobarbitone, quinalbarbitone and other drugs in man using the auditory flutter fusion threshold and the visual critical flicker fusion threshold. They also found phenobarbitone to be longer acting than quinalbarbitone. Their time courses were, however, more prolonged than those seen in the present study. Moreover, Besser & Duncan's results seem to indicate that phenobarbitone is at least at potent as quinalbarbitone, even over the initial 2 hours. So their findings also are somewhat at variance with those of the present study.

Eye movement and barbiturates. The site of barbiturate action on eye movement probably lies in the brain stem. At the sub-anaesthetic doses used there is suppression of smooth tracking, optokinetic nystagmus and convergence–divergence movements. Also, a small amplitude "gaze deviation nystagmus" is produced (Bergman *et al.*, 1952; Rashbass, 1959; Rashbass & Russell, 1961; Westheimer, 1963). Brain stem lesions in man are known to produce just this combination of defects (Jung & Kornhuber, 1964; Cogan, 1964). Some of these defects are reported to occur with lesions in the cerebral hemispheres but not the full combination. It is difficult to conceive how a peripheral drug action, say at the extraocular muscles, could produce such a combination of effects. Bender & Shanzer (1964) point out that the independently determined locations of the brain stem opto-motor system and of the reticular arousal systems are grossly the same. The particular susceptibility of the reticular arousal system to barbiturate action was shown by French, Verzeano & Magoun (1953).

With moderate doses smooth tracking shows similar susceptibility to that of subjective sedation and the two effects follow similar time courses. But tracking suppression is objectively quantifiable and provides good discrimination. Further investigation should determine which other types of drugs exert this effect and should clarify the relationship of opto-motor and hypno-sedative actions.

SUMMARY

1. Barbiturate suppression of smooth tracking eye movement was measured in man. The subjective drug effects were recorded.

2. The time courses of phenobarbitone, quinalbarbitone and pentobarbitone action were compared for 2 hr 12 min after oral administration. Subjects were starved for 5 hr previously to ensure rapid absorption.

3. Quinalbarbitone and pentobarbitone were found to be similar. Onset was rapid, reaching a peak about half an hour after administration. Phenobarbitone was found to have a more prolonged time course and to be two or three times less potent.

4. Redistribution within the body was thought to determine much of the decline in the effect of a moderate dose.

I thank Professor H. O. Schild and Dr. J. D. Montagu for their advice and help and Mr. N. W. Please for his generous aid and guidance in the least squares analysis. The work was supported by the Medical Research Council.

REFERENCES

BENDER, M. B. & SHANZER, S. (1964). Oculomotor pathways defined by electric stimulation and lesions in the brainstem of monkey. In *The Oculomotor System*, ed. Bender, M. B. New York: Harper and Row.

BERGMAN, P. S., NATHANSON, M. & BENDER, M. B. (1952). Electrical recording of normal and abnormal eye movements modified by drugs. *A.M.A. Archs Neurol. Psychiat.*, **67**, 357–374.

BESSER, G. M. & DUNCAN, CATHARINE (1967). The time course of action of single doses of diazepam, chlorpromazine and some barbiturates as measured by auditory flutter fusion and auditory flicker fusion thresholds in man. *Br. J. Pharmac. Chemother.*, **30**, 341–348.

BUSH, M. T. (1963). Sedatives and hypnotics: absorption, fate and excretion. In *Physiological Pharmacology*, ed. Root, W. S. & Hofmann, F. G. New York and London: Academic Press.

BUTLER, T. C. (1963). Duration of action of drugs as affected by tissue distribution. In *Metabolic Factors Controlling Duration of Drug Action*. (Proc. 1st Int. Pharmac. Meeting, Vol. 6), ed. Brodie, B. B. & Erdös, E. G. London: Pergamon.

BUTLER, T. C., MAHAFFEE, C. & WADDELL, W. J. (1954). Phenobarbital: Studies of elimination, accumulation, tolerance and dosage schedules. *J. Pharmac. exp. Ther.*, **111**, 425–435.

COGAN, D. G. (1964). Brain lesions and eye movements in man. In *The Oculomotor System*, ed. Bender, M.B. New York: Harper and Row.

DICKINS, D. W., LADER, M. H. & STEINBERG, H. (1965). Differential effects of two amphetamine—barbiturate mixtures in man. *Br. J. Pharmac. Chemother.*, **24**, 14–23.

FINNEY, D. J. (1964). *Statistical Methods in Biological Assay*, 2nd ed., pp. 99–138. London: Charles Griffin.

FRENCH, J. D., VERZEANO, M. & MAGOUN, H. W. (1953). A neural basis of the anaesthetic state. *A.M.A. Archs Neurol. Psychiat.*, **69**, 519–529.

GOODMAN, L. S. & GILMAN, A. (1965). *The Pharmacological Basis of Therapeutics*, 3rd ed., p. 107. New York: Macmillan.

GOODNOW, R. E., BEECHER, H. K., BRAZIER, M. A. B., MOSTELLER, F. & TAGUIRI, R. (1951). Physiological performance following a hypnotic dose of barbiturate. *J. Pharmac. exp. Ther.*, **102**, 55–61.

HINTON, J. M. (1961). The actions of amylobarbitone sodium, butobarbitone and quinalbarbitone sodium upon insomnia and nocturnal restlesness compared in psychiatric patients. *Br. J. Pharmac. Chemother.*, **16**, 82–89.

HINTON, J. M. (1963). A comparison of the effects of six barbiturates and a placebo on insomnia and motility in psychiatric patients. *Br. J. Pharmac. Chemother.*, **20**, 319–325.

HOGBEN, C. A. M., SCHANKER, L. S., TOCCO, D. J. & BRODIE, B. B. (1957). Absorption of drugs from the stomach: II. The human. *J. Pharmac. exp. Ther.*, **120**, 540–545.

JUNG, R. & KORNHUBER, H. H. (1964). Results of electronystagmography in man: The value of optokinetic, vestibular and spontaneous nystagmus for neurological diagnosis and research. In *The Oculomotor System*, ed. Bender, M. B. New York: Harper and Row.

KENDALL, M. G. & STUART, A. (1961). *The Advanced Theory of Statistics*, vol. 2, p. 75. London: Charles Griffin.

KORNETSKY, C., VATES, T. S. & KESSLER, E. K. (1959). A comparison of hypnotic and residual psychological effects of single doses of chlorpromazine and seconal in man. *J. Pharmac. exp. Ther.*, **127**, 51–54.

LASAGNA, L. (1956). A study of hypnotic drugs in patients with chronic diseases. *J. Chron. Dis.*, **3**, 122–133.

LATZ, A. & KORNETSKY, C. (1965). The effects of chlorpromazine and secobarbital under two conditions of reinforcement on the performance of chronic schizophrenic subjects. *Psychopharmacologia*, 7, 77–78.

MARK, L. C. (1963). Metabolism of barbiturates in man. *Clin. Pharmac. Ther.*, **4**, 504–530.

MAYNERT, E. W. & KLINGMAN, G. I. (1960). Acute tolerance to intravenous anaesthetics in dogs. *J. Pharmac. exp. Ther.*, **128**, 192–200.

RASHBASS, C. (1959). Barbiturate nystagmus and the mechanisms of visual fixation. *Nature, Lond.*, **183**, 897–898.

RASHBASS, C. (1961). The relationship between saccadic and smooth tracking eye movements. *J. Physiol., Lond.*, **159**, 326–338.

RASHBASS, C. & RUSSELL, G. F. M. (1961). Action of a barbiturate drug (amylobarbitone sodium) on the vestibulo-ocular reflex. *Brain*, **84**, 329–335.

RIGGS, D. S. (1963). *The Mathematical Approach to Physiological Problems*, pp. 149, 150. Baltimore: Williams and Wilkins.

SHACKEL, B. (1967). Electro-oculography. In *A Manual of Psychophysiological Methods*, ed. Venables, P. H. & Martin, I. Amsterdam: North-Holland.

SOLLMAN, T. (1957). *A Manual of Pharmacology*, 8th ed., p. 934. Philadelphia: Saunders.

WERNER, H. W., PRATT, T. W. & TATUM, A. C. (1937). A comparative study of several ultrashort-acting barbiturates, nembutal and tribromethanol. *J. Pharmac. exp. Ther.*, **60**, 189–197.

WESTHEIMER, G. (1963). Amphetamine, barbiturates and accommodation-convergence. *Archs Ophthal.*, **70**, 830–836.

WESTHEIMER, G. & RASHBASS, C. (1961). Barbiturates and eye vergence. *Nature, Lond.*, **191**, 833–834.