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A comparison of the central nervous system effects of haloperidol, chlorpromazine and sulpiride in normal volunteers

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1 Twelve healthy male volunteers participated in four experimental occasions during each of which they were dosed with one of the following anti-psychotic drugs: chlorpromazine (50 mg), haloperidol (3 mg), sulpiride (400 mg) and placebo. Drugs were allocated to subjects in a double-blind, crossover fashion.
2 The subject's mood state, psychometric performance and electroencephalogram (EEG) were assessed pre-dose, and at 2, 4, 6, 8, 24 and 48 h post-dose. Mood states were assessed using 16 visual analogue scales and psychomotor performance was measured using the following tests: elapsed time estimation, tapping rate, choice reaction times, a rapid information processing task, flash fusion threshold, a manipulative motor task, digit span, body sway and tremor.
3 Chlorpromazine and haloperidol significantly reduced subjective ratings of 'alertness' and 'contentedness', and haloperidol significantly reduced feelings of 'calmness'. Sulpiride did not significantly affect any of the visual analogue scales.
4 All three anti-psychotic drugs had similar EEG effects with peak effect 2 to 4 h post-dose. The profile was characterised by an increase in the proportion of slow wave activity (delta and theta) as well as decreased alpha (8–14 Hz) and faster (beta) wave activity.
5 Chlorpromazine reduced tapping rate and increased choice reaction movement times. Haloperidol reduced the flash fusion threshold frequency at 6 h post-dose. Sulpiride prolonged the duration of the manipulative motor task, particularly at 48 h post-dose.
6 All three anti-psychotic drugs impaired performance on the rapid information processing task. Chlorpromazine significantly reduced the number of correct letter pair identifications at 2, 4 and 6 h post-dose, haloperidol at 4, 6, 8, 24 and 48 h post-dose, and sulpiride at 24 h post-dose.
7 It is concluded that the EEG and the rapid information processing task are sensitive methods for detecting the central effects of anti-psychotic drugs in normal volunteers.

Keywords haloperidol chlorpromazine sulpiride psychomotor performance EEG

Introduction

Unlike the antidepressants or anxiolytics, there have been relatively few studies of the effects of anti-psychotic drugs on the central nevous system of normal volunteers. Those studies which have been reported, particularly with haloperidol, present conflicting data, with some statistically significant performance improvements and some significant impairments (Janke

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& Debus, 1972; Parrott & Hindmarch, 1975; Saletu *et al.*, 1983a,b).

Very few studies have compared the effects of different classes of anti-psychotic drugs on psychomotor performance. The purpose of the present study was to assess the effects of representative drugs from the three main chemical classes of anti-psychotics, namely a phenothiazine (chlorpromazine), a butyrophenone (haloperidol) and a benzamide (sulpiride). The doses chosen were all at the lower end of the therapeutic range for the treatment of schizophrenia. A wide range of measures of central nervous system function was employed, including the electroencephalogram, objective tests of performance and visual analogue scales.

Methods

Subjects

Twelve healthy male volunteers, aged 26 to 58 years and weighing 61 to 94 kg, were entered into the study. They gave their written informed consent and the protocol was approved by an independent Ethics Review Committee. Prior to the start of the study, all subjects underwent 10 separate training sessions on all the tests to reduce known practice effects (McClelland, 1987).

Experimental design

This was a double-blind, crossover study of single oral doses of chlorpromazine, 50 mg (Largactil; May & Baker), haloperidol, 3 mg (Seranace; Searle), sulpiride, 400 mg (Dolmatil; Squibb) and matched placebo. Doses were administered at approximately 10.00 h, on each study day, with an interval of at least 1 week between study days. The doses were randomly allocated to each study day for each volunteer. The volunteers performed a battery of tests predose and at 2, 4, 6, 8, 24 and 48 h post dose. Both the timing and content of meals and drinks were standardised on each study day.

Battery of tests

The battery of tests consisted of: subjective assessments from visual analogue scales, elapsed time estimation, tapping rate, choice reaction time, a rapid information processing task, flash fusion threshold and a manipulative motor task. All of these were presented by a CUBE microprocessor system as developed by McClelland *et al.* (1985). Body sway was measured by an ultrasound ranging device developed by Francis *et al.* (1986). The EEG and finger tremor were recorded and analysed by the method developed by McClelland & Shorter (1987). Digit span was also measured.

Visual analogue scales Sixteen bipolar visual analogue scales (Bond & Lader, 1974; Norris, 1971) were each presented to the volunteer on a visual display unit (VDU) as a 15 cm line bisected in the centre by a 2 cm line which acted as a cursor. Usually visual analogue scales are presented in paper-and-pencil form, and whilst some psychological tests do not transfer to an automated presentation (Bartram & Bayliss, 1984), automated visual analogue scales have been shown not to differ from the paper-and-pencil form (Hounslow *et al.*, 1987). Data are presented as hundredths of the total length of the line. The opposing ends of each line were labelled: alert/drowsy, strong/feeble, clear-headed/muzzy, well-coordinated/clumsy, energetic/lethargic, quick-witted/mentally slow, attentive/dreamy, proficient/incompetent, interested/bored, excited/calm, tense/relaxed, contented/discontented, tranquil/troubled, happy/sad, amicable/antagonistic, gregarious/withdrawn. Subjects were asked to move the cursor in either direction by pressing two buttons until it reached a point on each scale that represented how they felt at that moment with the extremes of the scales representing the 'most' they had ever experienced in their life before.

Elapsed time estimation Subjects pressed a button to initiate and then terminate their estimate of a 1 min period of elapsed time.

Tapping rate Subjects were asked to tap a morse key as fast as possible with one finger for a measured period of 1 min.

Choice reaction time Two coloured response buttons with adjacent light emitting diodes (LEDs) were mounted at an equal distance from a 'control' button. Upon illumination of one of the LEDs, subjects were asked to remove their preferred digit from the 'control' button and depress the appropriate button adjacent to the lit LED, as quickly as possible, then return the digit to depress the 'control' button until one of the LEDs was illuminated again. Two timings were recorded—(a) time taken to release the control button (i.e. the response time; with a predominantly cognitive component) and (b) the time taken to move and then depress the appropriate 'response' button adjacent to the

illuminated LED (i.e. the movement time, with a predominantly motor component).

During this task, subjects wore headphones through which a preparatory, or warning, tone was emitted prior to the illumination of one of the two LEDs. This tone was of two different pitches, each pitch being associated with one of the two LEDs for 80% of the duration of the test (consistent auditory cue) and associated with the other LED for 20% of the duration (inconsistent or misdirecting auditory cue).

There were a total of 100 stimuli, presented in a pseudorandom sequence such that the stimuli, both with and without auditory misdirection, were evenly distributed between the two LEDs.

Rapid information processing This task required the subjects to sustain a continuous level of performance over a period of 400 s. Five different letters of the alphabet (A, B, D, E and H), in both lower and upper cases, were presented one at a time on a VDU in pseudorandom order. Four hundred presentations were made at the rate of 1 s^{-1}, and each display lasted for 0.1 s. There were 20 occasions when the same letter was presented consecutively in the same case, and 20 when the same letter was presented consecutively in different cases. The subject was asked to depress a response button as soon as he had identified consecutive presentations of the same letter, irrespective of case. This method is a development of the work of Posner & Keele (1967),

Flash fusion threshold A LED was mounted at the end of a sealed oscilloscope viewing hood. This LED was illuminated twice, the interval between the flashes varying in an apparently random fashion under microprocessor control. The subject was asked to press one button if he perceived one flash and another button if he perceived two flashes. A total of 100 presentations were made covering a range of interflash intervals of 25 to 124 ms. This method is based on that of Venables (1963) and Gruzelier & Corballis (1970).

Manipulative motor task Subjects used large forceps to transfer 36 glass beads (1.5–2 mm diameter) one at a time, from a petri dish into individual wells of a microtitre plate. The subject timed the task by pressing a button before commencing and immediately after finishing the task.

Body sway Both lateral and sagittal body sway were measured for a period of 1 min with the subject standing with his eyes closed. Two ultrasonic transducers (Polaroid) placed at right-angles some 70 cm from the body at a height of 130 cm were used as ranging units. A burst of ultrasonic pulses was emitted from each transducer alternately. The time taken for these pulses to travel to the subject and return to the transducer was measured electronically. As the subject-to-transducer path length varies, so does the time of travel of the ultrasonic pulses. This system, developed by Francis *et al.* (1986), converted the information into an analogue voltage output which was proportional to the distance of the subject from the tranducer.

The output from the system was recorded on magnetic tape and later replayed into a DEC PDP 11/40 minicomputer, analysed using Fourier analysis and presented as total power of frequencies slower than 20 cycles per minute.

EEG Silver/silver chloride electrodes were placed on the scalp according to the International Federation 10–20 system at 0_2, A_2, FP_1, and FP_2. The signals from 0_2-A_2 and FP_1-FP_2 were differentially amplified (HDX 82; Oxford Medical Systems) then passed via an isolator amplifier (FE-265-1A; Fylde) and displayed on an oscilloscope. The signal from FP_1-FP_2 was used to help identify artefacts and exclude them from computer analysis. The signal 0_2-A_2 was digitised by a 12 BIT analogue to digital converter (Cambridge Microprocessor Systems) then passed to a BBC microcomputer with a second 6502 processor (Acorn).

Sixteen 10 s samples, each of 1024 points, were analysed from each subject at each recording time. Primary wave analysis, derived from zero-crossing, was performed and portrayed as the percent time in each 2 Hz band up to 30 Hz. Zero crossing analysis was also performed on the first derivative of the EEG and displayed in 4 Hz bands up to 60 Hz. The power spectrum, in 2 Hz bands up to 30 Hz, was derived from a Fast Fourier Transform of the EEG. For each subject the post-dose value was compared with the pre-dose and the resultant ratios averaged to give a geometric mean and standard error. The Spectral Difference Index was calculated from the relative power in each 1 Hz band and analysed by one-tailed Student's *t*-test, as described by Irwin (1982).

Tremor A piezo-electric tranducer (Dantec) was secured to the middle finger of the subject's non-dominant hand. The subject was seated in a chair with the forearm supported from elbow to wrist and the hand held out in line with the forearm for a recording period of 4 min. The

resultant signal from the transducer was amplified and analysed using the method described above for the EEG, except that only eight samples were analysed at each recording time and the analysis was restricted to use of the Fast Fourier Transform.

Digit span A seven-digit sequence of numbers was read aloud to the subject who was asked to write it down immediately after all the digits had been read and guessing any digit he could not recall. The process was repeated with eight, nine and ten digit numbers.

The test was scored by counting as correct only those sequences of numbers in which every digit was correct and in the correct position. If one sequence was wrong but a longer sequence was correct, an appropriate score was awarded based on a pre-determined scoring system (e.g. if the seven and nine digit sequences were correct, but the eight digit sequence was wrong, the score awarded was 8).

Statistical analysis

Unless otherwise stated, all data were analysed by the Wilk-Shapiro test for normality and in the absence of a significant deviation from the normal distribution, by analysis of variance. Where the analysis of variance revealed a statistically significant drug effect, the Newman-Keul's multiple range test was used to determine individual differences.

Results

Visual analogue scales

Statistically significant drug effects were found on all of the sixteen visual analogue scales at 4, 6 and 8 h post-dose. Peak effects of haloperidol and chlorpromazine were at 4 h post-dose; the mean scores at this time are shown in Table 1. Sulpiride did not significantly differ from placebo at any timepoint. The effect of both haloperidol and chlorpromazine was to shift the mean score towards the less socially acceptable end of the scale (Bond & Lader, 1974).

Elapsed time estimation

There were no statistically significant drug effects on the estimate of a 1 min period of elapsed time.

Tapping rate

Chlorpromazine significantly reduced the number of morse key taps in a 1 min period at 2 h post-dose compared with placebo (Figure 1). By 8 h post-dose, the mean number of taps after chlorpromazine treatment approximated to placebo values. None of the other treatments differed significantly from placebo at any timepoint.

Table 1 Effects of chlorpromazine, haloperidol and sulpiride on visual analogue scales at 4 h post-dose

0	100	Placebo	*Chlorpromazine 50 mg*	*Haloperidol 3 mg*	*Sulpiride 400 mg*
Alert	Drowsy	39	56*	51	38
Attentive	Dreamy	35	51*	45	37
Energetic	Lethargic	38	52*	49*	37
Clear-headed	Muzzy	37	51*	45	38
Well-coordinated	Clumsy	36	48*	44*	36
Quick-witted	Mentally-slow	35	50*	44	36
Strong	Feeble	33	48*	45*	36
Interested	Bored	38	51*	50*	38
Proficient	Incompetent	34	44*	43*	35
Happy	Sad	30	36	42*	32
Amicable	Antagonistic	30	34	41*	33
Tranquil	Troubled	31	37	44*	34
Contented	Discontented	30	39*	45*	30
Gregarious	Withdrawn	33	43*	41*	35
Calm	Excited	30	36	39*	32
Relaxed	Tense	30	35	42*	35

*$P < 0.05$ difference from placebo.

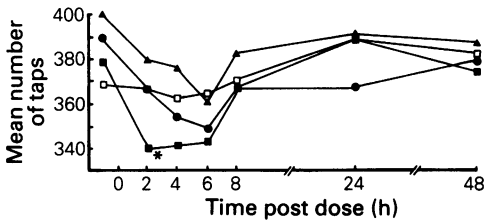

Figure 1 Effects of placebo (□), haloperidol (▲), chlorpromazine (■) and sulpiride (●) on the number of morse key taps in a 1 min period. *$P < 0.05$ difference from placebo.

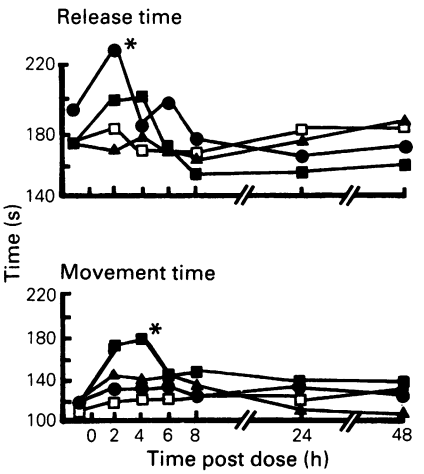

Figure 2 Effects of placebo (□), haloperidol (▲), chlorpromazine (■) and sulpiride (●) on a choice reaction task, with a consistent auditory cue. *$P < 0.05$ difference from placebo.

Choice reaction time Chlorpromazine tended to prolong the movement time on the choice reaction task both with and without auditory misdirection. This was significantly different from placebo at 4 h post-dose with a consistent auditory cue (Figure 2). Sulpiride did not affect movement times but did tend to prolong the release time, being statistically significantly different from placebo 2 h post-dose, with a consistent auditory cue. Haloperidol did not significantly affect any of the variables measured on this task.

Rapid information processing task

All three drugs had a statistically significant effect on the rapid information processing task (Figure 3). Chlorpromazine significantly reduced

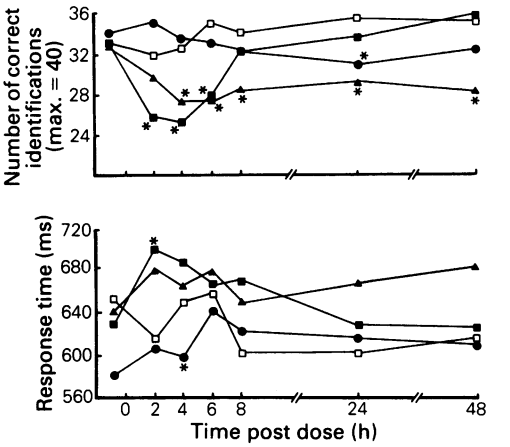

Figure 3 Effects of placebo (□), haloperidol (▲), chlorpromazine (■) and sulpiride (●) on the response time and number of correct concurrent pair identifications on a rapid information processing task. *$P < 0.05$ difference from placebo.

the number of correct identifications of consecutive presentations of the same letter at 2, 4 and 6 h post-dose, and significantly prolonged the response time at 2 h post-dose. Haloperidol significantly reduced the number of positive identifications at 4, 6, 8, 24 and 48 h after dosage. Sulpiride significantly reduced the number of positive identifications at 24 h post-dose and significantly improved the response time at 4 h post-dose; however, pre-dose, the sulpiride treatment did show faster response times than with the other treatments, although this difference was not statistically significant.

Flash fusion threshold

The only statistically significant difference from placebo was observed 6 h after treatment with haloperidol when the threshold was reduced (i.e. haloperidol improved the ability to discriminate a pair of light flashes from an apparently fused light source).

Manipulative motor task

Sulpiride tended to prolong the duration of the manipulative motor task at 24 h post-dose and significantly prolonged the task duration at 48 h post-dose (Figure 4). The other two drug treatments did not significantly affect task duration.

Body sway

None of the drug treatments significantly affected body sway in the sagittal plane. The only statisti-

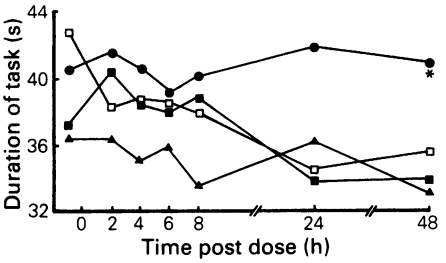

Figure 4 Effects of placebo (□), haloperidol (▲), chlorpromazine (■) and sulpiride (●) on the duration of a manipulative motor task. *$P < 0.05$ difference from placebo.

cally significant treatment effect on lateral body sway occurred at 6 h post-dose, when all three drugs apeared to reduce the amount of sway. However, this statistical significance is probably an artefact, resulting from the placebo treatment showing an increase in sway.

EEG

The time course of the EEG drug effects are shown in Figure 5. Both chlorpromazine and haloperidol showed clear, statistically significant effects 2–6 h post-dose. Sulpiride had a less pronounced EEG effect, with just a trend towards a difference from placebo at 4 h post-dose.

The results of primary wave, first derivative and Fourier analyses at 4 h post-dose are shown in Figure 6. All three drugs increased the slow delta and theta activity (< 8 Hz) and decreased the alpha activity (8–14 Hz) compared with placebo. Both chlorpromazine and haloperidol decreased the fast beta activity (> 20 Hz), whereas sulpiride tended to increase it.

Tremor

There were no consistent drug-related effects on the Fourier power spectrum of tremor.

Digit span

There were no statistically significant treatment effects on digit span.

Discussion

Haloperidol is a long established member of the butyrophenone class of drugs which has been widely used in clinical practice. However, there have been few studies on the effects of butyrophenones in normal subjects and the available data is inconsistent. Parrott & Hindmarch (1975) reported a statistically significant impairment in the ability to distinguish a flickering from an apparently fused light source but found a tendency for performance on a choice reaction time task to be improved, after a single oral dose of 1 mg haloperidol. Saletu *et al.* (1983a,b) found a significant improvement in performance on a choice reaction time task, impaired attention,

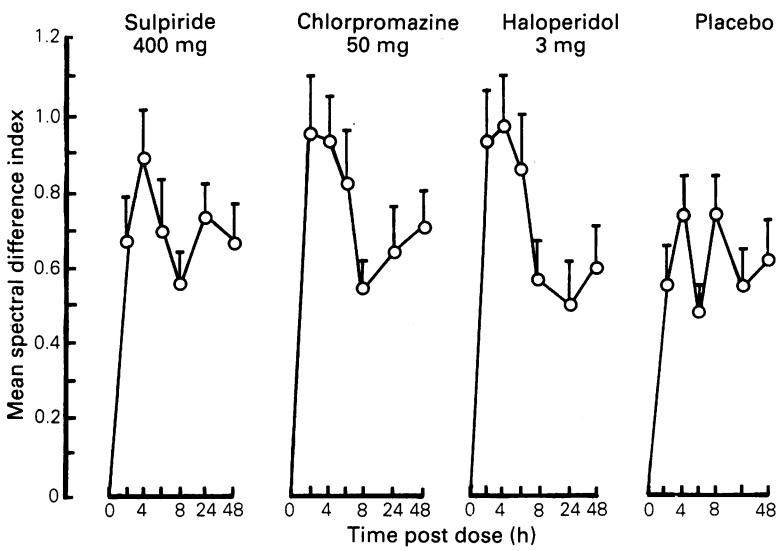

Figure 5 Effects of placebo (□), haloperidol (▲), chlorpromazine (■) and sulpiride (●) on the EEG spectral difference index (mean ± s.e. mean). *$P < 0.05$ difference from placebo.

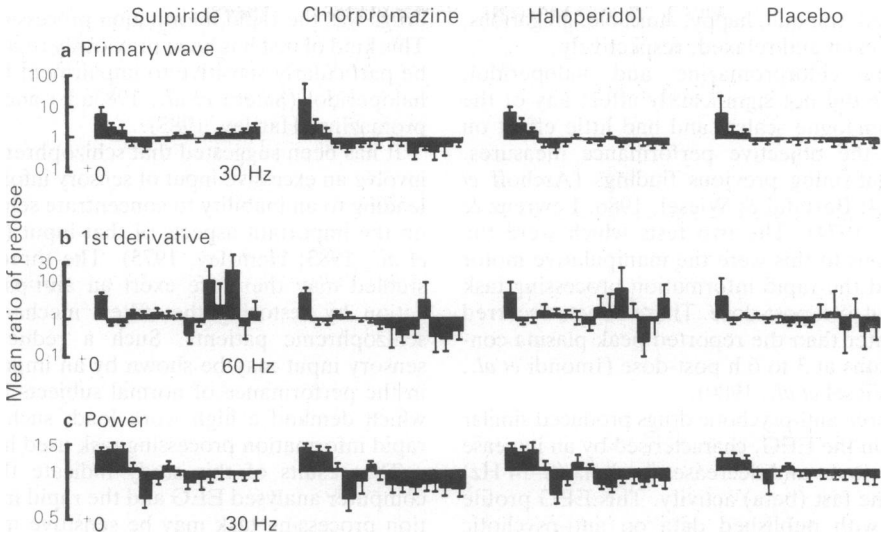

Figure 6 Effects of placebo, haloperidol, chlorpromazine and sulpiride on the computer analysed EEG at 4 h post-dose.

and no drug effect on flicker fusion after a 2 mg oral dose of haloperidol. Janke & Debus (1972) have shown that haloperidol (1 and 2 mg orally) can produce an improvement in performance under low work load conditions, which can be partly reversed under a high work load.

In the study carried out here with an oral dose of 3 mg, and a fairly intensive study design (high work load), haloperidol affected several objective measures of performance, confirming our previous study with this dose of haloperidol on the same test battery (McClelland *et al.*, 1987). The improved ability to discriminate on the flash fusion threshold does however, conflict with the flicker fusion results of Parrott & Hindmarch (1975). The objective performance test which was most clearly affected by haloperidol was the rapid information processing task. Performance on this test was still significantly impaired 48 h after dosage. It is unusual for a psychotropic drug to produce such a prolonged effect in normal subjects after a single oral dose. This effect does however confirm our previous findings of a statistically significant effect persisting for at least 24 h on this test after this dose of haloperidol (McClelland *et al.*, 1987). This is therefore unlikely to be a chance finding. The plasma half-life of haloperidol in normal subjects has been reported to be between 12 and 38 h (Forsman & Öhman, 1976). The effect of haloperidol on the rapid information processing task may therefore correlate with its pharmacokinetics.

Although haloperidol clearly affected the rapid information processing task it did not affect any of the measures of motor ability or speed. This would suggest that haloperidol must be exerting its effect on the stimulus perception or central processing.

Chlorpromazine was the most sedative drug used in this study, impairing performance on tapping rate, choice reaction times, rapid information processing and visual analogue scales. This confirms the significant impairment previously reported (Mirsky & Kornetsky, 1964; Parrott & Hindmarch, 1975; Tecce *et al.*, 1975). However, unlike Besser & Duncan (1967), Parrott & Hindmarch (1975) and Gruzelier & Corballis (1970), this study did not show any impairment of discrimination by chlorpromazine during the flash fusion threshold (or flicker fusion threshold) test. The time course of the effects of chlorpromazine appear to correlate well with the reported peak plasma concentration of chlorpromazine 2–4 h post-dose (Baldessarini, 1980).

Although both chlorpromazine and haloperidol significantly affected many of the visual analogue scales, there were quantitative differences between the two drugs. Chlorpromazine tended to shift negatively the mean scores of the nine scales which form the 'alertness' factor described by Bond & Lader (1974), these being the scales for alert, strong, clear-headed, well-coordinated, energetic, quick-witted, attentive, proficient and interested. Haloperidol caused negative shifts of mean scores in the 'contentedness' and 'calmness' factors, these being the scales for

contented, tranquil, happy, amicable, gregarious, and for calm and relaxed, respectively.

Unlike chlorpromazine and haloperidol, sulpiride did not significantly affect any of the visual analogue scales, and had little effect on any of the objective performance measures, thus confirming previous findings (Aschoff *et al.*, 1974; Bartafai & Wiesel, 1986; Lewrenz & Kempe, 1974). The two tests which were the exceptions to this were the manipulative motor task and the rapid information processing task at 24 and 48 h post-dose. These effects occurred much later than the reported peak plasma concentrations at 3 to 6 h post-dose (Imondi *et al.*, 1978; Wiesel *et al.*, 1980).

All three anti-psychotic drugs produced similar effects on the EEG, characterised by an increase in slow waves and decreases in alpha (8–14 Hz) and some fast (beta) activity. This EEG profile agrees with published data on anti-psychotic drugs (Fink, 1969; Herrmann, 1982; Itil *et al.*, 1979; Weineke *et al.*, 1981).

The only other test in this battery which was significantly affected by all three anti-psychotic drugs was the rapid information processing task. This kind of test has been previously reported to be particularly sensitive to impairment by both haloperidol (Saletu *et al.*, 1983a,b) and chlorpromazine (Hartley, 1983).

It has been suggested that schizophrenia may involve an excessive input of sensory information leading to an inability to concentrate selectively on the important aspects of that input (Gelder *et al.*, 1983; Hemsley, 1975). The three drugs studied may therefore exert an anti-psychotic action by restoring the 'filter' mechanism in schizophrenic patients. Such a reduction in sensory input may be shown by an impairment in the performance of normal subjects in tasks which demand a high work load, such as the rapid information processing task used here.

The results of this study indicate that the computer analysed EEG and the rapid information processing task may be sensitive methods of studying the relative potency and time course of central nervous system effects of anti-psychotic drugs in healthy volunteers.

References

Aschoff, von J. C., Bechar, W. & Weinert, D. (1974). Computer-nystagmography, a new method of determining changes in vigilance as a response to psychotropic drugs. *Arzneim.-Forsch.*, **24**, 1085–1087.

Baldessarini, R. J. (1980). Drugs and the treatment of psychiatric disorders. In *The pharmacological basis of therapeutics*, 6th edition, eds Goodman Gilman, A., Goodman, L. S. & Gilman, A. New York: Macmillan.

Bartafai, A. & Wiesel, F.-A. (1986). Effect of sulpiride on vigilance in healthy subjects. *Int. J. Psychophysiol.*, **4**, 1–5.

Bartram, D. & Bayliss, R. (1984). Automated testing: past, present and future. *J. occupational Psychology*, **57**, 221–237.

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

Bond, A. J. & Lader, M. H. (1974). The use of analogue scales in rating subjective feelings. *Br. J. med. Psychol.*, **47**, 211–218.

Fink, M. (1969). EEG and human psychopharmacology. *Ann. Rev. Pharmac.*, **9**, 241–258.

Forsman, A. & Öhman, R. (1976). Pharmacokinetic studies on haloperidol in man. *Curr. Ther. Res.*, **20**, 319–336.

Francis, G. R., McClelland, G. R. & Pettitt, K. E. E. (1986). Measurement of body sway using ultrasound. *Br. J. clin. Pharmac.*, **21**, 123P.

Gelder, M. G., Gath, C. & Mayou, R. (1983). *Oxford textbook of psychiatry*. Oxford: Oxford University Press.

Gruzelier, J. H. & Corballis, M. C. (1970). Effects of instructions and drug administration on temporal resolutions of paired flashes. *Quart. J. exp. Psychol.*, **22**, 115–124.

Hartley, L. R. (1983). Arousal, temporal and spatial uncertainty and drug effects. *Prog. Neuro-Psychopharmac. Biol. Psychiat.*, **7**, 29–37.

Hounslow, N. J., Tamrasians, S., Wiseman, W. T., Mann, S. & Van den Burg, M. J. (1987). Use of a visual analogue meter. *Br. J. clin. Pharmac.*, **23**, 117P–118P.

Hemsley, D. R. (1975). A two-stage model of attention in schizophrenia research. *Br. J. Soc. clin. Psychol.*, **14**, 81–89.

Herrmann, W. M. (1982). Development and critical evaluation of an objective procedure for the electroencephalographic classification of psychotropic drugs. In *Electroencephalography in drug research*, ed. Herrmann, W. M. London: Butterworths.

Imondi, A. R., Alan, A. S., Brennan, J. J. & Hagermann, L. M. (1978). Metabolism of sulpiride in man and Rhesus monkeys. *Arch. int. Pharmac.*, **232**, 79–91.

Irwin, P. (1982). Spectral difference index: a single EEG measure of drug effect. Electroencephology. *Clin. Neurophysiol.*, **54**, 342–346.

Itil, T. M., Shapiro, D. M., Herrmann, W. M., Schultz, W. & Morgan, V. (1979). HZI systems for EEG parametrization and classification of psychotropic drugs. *Pharmacopsychiatry*, **12**, 4–19.

Janke, W. & Debus, G. (1972). Double-blind psychometric evaluation of pimozide and haloperidol *versus* placebo in emotionally stable volunteers under two different work load conditions. *Pharmacopsychiatry*, **1**, 34–51.

Lewrenz, H. & Kempe, P. (1974). Psychologische Untersuchungen nach Dogmatil-Applikation. *Münch. med. Wschr.*, **116**, 583–584.

McClelland, G. R. (1987). The effects of practice on measures of performance. *Human Psychopharmac.*, **2**, 109–118.

McClelland, G. R. & Shorter, J. H. (1987). A microcomputer based system for the acquisition and analysis of electroencephalographic (EEG) data. *Br. J. clin. Pharmac.*, **23**, 124P–125P.

McClelland, G. R., Semple, J. M., Shorter, J. H. & Waterfield, S. (1985). Use of microprocessor technology in a test battery for psychopharmacological volunteer studies. *Br. J. Pharmac.*, **84**, 202P.

McClelland, G. R., Cooper, S. M. & Raptopoulos, P. (1987). Paroxetine and haloperidol: effects on psychomotor performance. *Br. J. clin. Pharmac.*, **24**, 268P.

Mirsky, A. F. & Kornetsky, C. (1964). On the dissimilar effects of drugs on the digit symbol substitution and continuous performance tests. A review and preliminary integration of behavioural and physiological evidence. *Psychopharmacologica*, **5**, 161–177.

Norris, H. (1971). The action of sedation on brainstem oculomotor systems in man. *Neuropharmac.*, **10**, 181–191.

Parrott, A. C. & Hindmarch, I. (1975). Haloperidol and chlorpromazine – comparative effects on arousal and performance. *IRCS med. Sci.*, **3**, 562.

Posner, N. I. & Keele, S. W. (1967). Decay of visual information from a single letter. *Science*, **158**, 137–139.

Saletu, B., Grünberger, J., Linzmayer, L. & Dubini, A. (1983a). Determinations of pharmacodynamics of the new neuroleptic zetidoline by neuroendocrinologic, pharmaco-EEG and psychometric studies – Part I. *Int. J. clin. Pharmac. Ther. Tox.*, **21**, 489–495.

Saletu, B., Grünberger, J., Linzmayer, L. & Dubini, A. (1983b). Determination of the pharmacodynamics of the new neuroleptic zetidoline by neuroendocrinologic, pharmaco-EEG, and psychometric studies. Part II. *Int. J. clin. Pharmac. Ther. Tox.*, **21**, 544–551.

Tecce, J. T., Cole, J. O. & Bowman, J. S. (1975). Chlorpramazine effects on brain activity and reaction time in normal women. *Psychopharmacology*, **43**, 293–259.

Venables, P. H. (1963). Selectivity of attention, withdrawal and cortical activation. Studies in chronic schizophrenia. *Arch. gen. Psychiat.*, **9**, 74–78.

Weineke, G. H., Verhoeven, W. M. A., Westenberg, H. M. G., de Wilde, H., Lopas da Silva, F. H., van Praag, H. M. & Storm van Leeuwen, W. (1981). The effects of haloperidol on the EEG spectrum. *Psychopharmacology*, **74**, 33–34.

Wiesel, F. A., Alfredsson, G., Ehrnebo, M. & Sedvall, G. (1980). The pharmacokinetics of intravenous and oral sulpiride in healthy human subjects. *Eur. J. clin. Pharmac.*, **17**, 385–391.

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