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The Effect of Neuroleptics on Cognitive and Psychomotor Function
A Preliminary Study in Healthy Volunteers

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The effects of haloperidol (1 mg), benzhexol (5 mg), diazepam (10 mg) and caffeine (400 mg) on subjective and objective measures of cognitive and psychomotor function were compared with placebo in 20 healthy volunteers. While both diazepam and benzhexol were associated with highly significant impairments in subjective alertness, critical flicker fusion threshold and choice reaction time (CRT), haloperidol could not be distinguished from placebo in most tests but was actually associated with an apparent improvement in CRT (in males) and simple visual reaction time. The perceptual maze test detected impairment by benzhexol on processing speed but was not sensitive to any other drug effects. Multiple-dose studies are required to establish if there is a true activating effect of haloperidol using a test of sustained attention. No effect of Eysenck personality subtype or life events on baseline or drug response data was detected.

Studies of the effect of neuroleptics on cognitive and psychomotor function are necessary to elucidate the psychophysiological mechanisms involved in their therapeutic effect. However, studies in patients are confounded by their clinical state and variable levels of motivation, while inconsistent results have been reported in healthy volunteers as a result of variable tests and experimental designs (for review see King, 1990).

Generalised impairments in psychomotor function with relative sparing of cognition, or impaired performance on paced tests of sustained attention, have usually been reported after single doses of chlorpromazine (e.g. Mirsky & Kornetsky, 1964). However, non-sedative phenothiazines such as trifluoperazine and perphenazine were found to cause improvements in some measures of psychomotor performance, even after doses of up to 16 mg in normal volunteers (DiMascio *et al*, 1963*a*,*b*), and haloperidol was reported to improve cognitive function in tests such as the digit symbol substitution test (DSST) (James & James, 1973), choice reaction time (CRT) response latency (Parrott & Hindmarch, 1975), and in some simple and complex reaction time tasks (Saletu *et al*, 1983*a*,*b*).

Accordingly, we decided to compare haloperidol with two standard positive controls, diazepam for impairments (Linnoila *et al*, 1983; Ghoneim *et al*, 1984) and caffeine for possible improvements (Fagan *et al*, 1988; Zwyghuizen-Doorenbos *et al*, 1990) in function, and with placebo, in healthy volunteers. We also included an anticholinergic drug, since these are frequently combined with neuroleptics in clinical practice and previous clinical studies did not appear to have controlled for their effect. We chose benzhexol as a commonly prescribed, relatively selective anticholinergic which had previously been shown to produce significant impairments in a group of non-demented elderly patients (Potamianos & Kellet, 1982).

In addition to a standard psychomotor function test battery we also wished to test whether the perceptual maze test (PMT), incorporated in an automated psychological assessment system (APAS) by Elithorn and Lavander (Elithorn *et al*, 1982) as a measure of cognitive function, would detect neuroleptic drug effects. This test requires continuous attention because 16 progressively more difficult mazes, which can take up to 30 minutes to complete, are included in each session. It has been shown to have both problem-solving and visuo-spatial components, and is associated with increased metabolic activity in the left frontal area and both occipital poles, in positron emission tomographic studies (Nybäck *et al*, 1985).

Finally, we also decided to try to control for possible psychosocial influences on drug response by completion of a personality questionnaire and the recording of recent life events.

Method

Ten male and 10 female normal healthy volunteers, aged 19–27 (mean 21.8) years, weighing 51.5–89.5 (mean 64.48) kg, who had given written informed consent, were each given single doses of haloperidol (1 mg), benzhexol (5 mg), diazepam (10 mg), caffeine (400 mg), or placebo (lactose), at weekly intervals in a double-blind, randomised order. The tablets were given by a research nurse not involved in carrying out any of the tests. The study was approved by the Queen's University, Faculty of Medicine Research Ethical Committee. Volunteers were excluded if there was a history of any of the following: cardiovascular,

respiratory, hepatic or renal disease, allergy or hypersensitivity to any drug; psychiatric or neurological disease; drug abuse or drug ingestion 14 days before the study. None of the volunteers were heavy smokers: nine were non-smokers, five smoked less than ten cigarettes/day, five (three males and two females) smoked ten cigarettes/day and one (female) 15 cigarettes/day. Smoking was not permitted on study days. The volunteers were asked to abstain from alcohol for three days before each study day and drinks or food containing caffeine for 12 hours before and throughout each study day. They were allowed one cup of a non-caffeine drink before the start of the study. Breakfast and a light standardised lunch were provided during each study day, but tea, cocoa, coffee, cola drinks and chocolate were not permitted until after the 24-hour readings on the following day. Volunteers always returned home by public transport or taxi, and were not permitted to drive on study days.

Before the study, each volunteer had a complete physical examination, completed the Eysenck Personality Questionnaire (EPQ), had at least two pre-study practice sessions, not more than one week apart, on the psychomotor tests, and their general practitioners were asked to inform us if they knew of any reason why a volunteer should not take part in such a study. At the start of each study day each volunteer completed a life-event rating scale covering events considered significant in the previous week.

Subjective feelings and moods were assessed using 16 visual analogue rating scales (VARS) (Norris, 1971). Critical flicker fusion threshold (CFFT) and choice reaction time (CRT) were measured using the Leeds Psychomotor Tester (Hindmarch, 1975). CFFT was the mean of six runs, three with ascending and three with descending flicker frequency, and the CRT was the mean of 25 trials taken after five practice trials on each occasion. A further six neuropsychological and psychomotor tests were measured using an automated psychological assessment system (APAS) for use with an Apple IIe microcomputer, devised by Elithorn and Lavander (Elithorn *et al*, 1982). This included: five measures of *finger tapping* speed (right, left, alternating fingers on the right, alternating fingers on the left, alternating right and left forefingers); *simple auditory* and *visual reaction times*; a *visual two-choice reaction time* (left, right, and error score); *trail making* (three versions of a fine motor co-ordination task); and the *perceptual maze test* (PMT) (Smith *et al*, 1978), which gave five measures – 'search' or 'thinking time', processing speed (nodes/second), motor time, errors, and right/left bias in solving these visuo-spatial tasks. The APAS thus yielded a total of 18 measures and took an average of approximately 20 minutes to complete.

After an overnight fast from 10.00 p.m. on the day before each study day each volunteer had baseline assessments of VARS, CFFT and CRT followed by the study medication given by a research nurse not involved in the assessment procedures. These tests were repeated at 1, 2, 3, 6 and 24 hours, and the APAS administered between four and five hours after medication. Standardised non-caffeine breakfast snacks and light lunches were given after the one-hour and three-hour readings respectively. The volunteers were not permitted to drive after the study and returned home by taxi or public transport.

Apart from the APAS data, neither the variances in the raw data nor their log-transformations were homogeneous, and were, therefore, analysed by non-parametric procedures. For the CFFT and CRT data, following Friedman two-way analyses of variance ($P<0.02$) significant differences between drugs were identified using a method for multiple comparisons based on the differences between ranks (Conover, 1980). For the VARS and EPQ data, Friedman ANOVAs were followed by Wilcoxon and Mann–Whitney *U*-tests, respectively. Because of both wide intra- and inter-personal baseline differences in the CFFT and CRT data (see Tables 1 and 2), the statistical analyses were carried out on percentage changes from baseline. Three-way parametric ANOVAs were applied to the APAS log-transformed data. Male and female groups were combined if there were no statistically significant differences between them.

Results

Visual analogue rating scales (VARS)

Using a principal component factor analysis, Bond & Lader (1974) showed that the 16 Norris VARS consisted of three dimensions: alertness (nine scales), contentedness (five scales) and calmness (two scales). Thus, only the scales with the highest loadings for each of these factors (viz alert–drowsy; happy–sad; calm–excited) were analysed statistically, and statistically significant changes were found with only one of these (alert–drowsy). As shown in Fig. 1, compared with placebo, both diazepam (10 mg) and benzhexol (5 mg) caused significant drowsiness at one and two hours after dosing ($P<0.01$).

Table 1
Critical flicker fusion threshold (CFFT). Raw data (means (s.d.)) for total group ($n=20$)

	Time: hours					
	0	1	2	3	6	24
Placebo	32.43 (4.67)	32.50 (4.47)	32.40 (4.77)	32.67 (4.60)	32.50 (4.82)	32.66 (4.99)
Haloperidol	33.06 (5.22)	33.35 (5.12)	32.91 (4.95)	32.92 (5.29)	32.45 (5.52)	32.39 (5.32)
Benzhexol	33.31 (4.88)	32.68 (3.87)	32.41 (4.58)**	32.77 (4.04)	32.51 (4.78)	32.43 (5.23)
Diazepam	32.12 (5.23)	30.65 (4.38)***	30.39 (4.55)****	31.35 (4.75)	31.47 (5.00)	32.17 (5.36)
Caffeine	33.17 (5.17)	32.75 (4.80)*	32.78 (5.23)	32.93 (5.16)	32.63 (5.30)	32.77 (5.65)

Percentage change from baseline, different from placebo, *$P<0.05$; **$P<0.02$; ***$P<0.005$; ****$P<0.001$.

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Table 2
Choice reaction time (CRT). Raw data (means (s.d.)) for males ($n = 10$) and females ($n = 10$)

	Time: hours											
	0		1		2		3		6		24	
	men	women	men	women	men	women	men	women	men	women	men	women
Latency: ms												
Placebo	342 (63)	336 (49)	340 (57)	342 (68)	344 (71)	346 (63)	373 (69)	345 (61)	356 (77)	336 (66)	340 (54)	334 (61)
Haloperidol	347 (53)	337 (40)	337 (35)	332 (43)	332 (43)	362 (53)	331 (50)	347 (57)	333 (47)	354 (49)	341 (66)	341 (42)
Benzhexol	339 (49)	339 (39)	383 (56)****	374 (65)	392 (86)***	375 (60)	361 (53)	347 (52)	365 (72)	345 (46)	340 (60)	356 (50)
Diazepam	346 (60)	345 (42)	372 (64)*	391 (110)	364 (61)	366 (38)	363 (49)	356 (27)	347 (53)	347 (51)	338 (66)	340 (53)
Caffeine	338 (52)	334 (54)	340 (53)	346 (56)	341 (37)	351 (58)	346 (49)	355 (65)	362 (72)	354 (56)	349 (58)	340 (66)
Motor movement: ms												
Placebo	175 (61)	213 (59)	187 (79)	216 (67)	185 (73)	220 (69)	189 (90)	215 (59)	176 (78)	223 (60)	184 (83)	222 (60)
Haloperidol	161 (67)	205 (64)	171 (83)	211 (75)	168 (65)	210 (67)	170 (64)	221 (59)	165 (69)	229 (64)	155 (65)	213 (69)
Benzhexol	176 (72)	206 (73)	196 (77)	230 (81)	189 (77)	230 (68)	184 (70)	227 (60)	166 (80)	227 (54)*	178 (82)	221 (69)
Diazepam	191 (86)	217 (64)	244 (146)	270 (110)	192 (77)	242 (60)	184 (84)	220 (65)	163 (86)	224 (54)	177 (101)	204 (49)
Caffeine	161 (73)	242 (109)	164 (80)	190 (46)*	172 (102)	203 (50)*	170 (86)	201 (54)	177 (99)	194 (69)	184 (76)	197 (66)
Total: ms												
Placebo	517 (107)	549 (87)	525 (115)	557 (114)	529 (125)	566 (116)	562 (141)	560 (96)	532 (142)	560 (108)	524 (122)	556 (94)
Haloperidol	507 (104)	542 (90)	508 (104)	543 (104)	500 (87)	564 (105)	501 (104)**	568 (107)	497 (101)	583 (107)	496 (126)	554 (95)
Benzhexol	515 (102)	545 (101)	580 (118)****	604 (132)**	581 (139)****	605 (107)*	545 (109)	574 (96)	530 (128)	567 (96)	518 (131)	575 (108)
Diazepam	536 (119)	562 (94)	626 (197)	661 (204)*	556 (122)	608 (90)*	547 (121)	576 (86)	510 (126)	571 (94)	515 (146)	553 (91)
Caffeine	500 (116)	566 (144)	504 (124)	530 (78)	513 (128)	553 (95)	516 (119)	556 (99)	539 (157)	548 (116)	533 (122)	537 (118)

Percentage change from baseline, different from placebo, *$P<0.05$; **$P<0.02$; ***$P<0.01$; ****$P<0.005$.

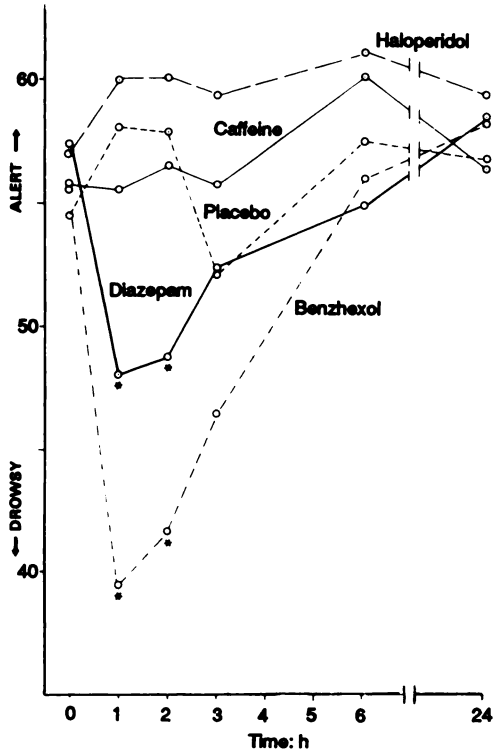

Fig. 1 Mean raw scores on visual analogue rating scale for subjective alertness in 20 healthy volunteers (10 males and 10 females). Diazepam (10 mg) and benzhexol (5 mg) caused significant drowsiness compared with placebo at one and two hours after dosing (*$P<0.01$).

Critical flicker fusion threshold (CFFT)

Male and female groups could be combined for the CFFT data which were highly significantly decreased at one ($P<0.005$) and two ($P<0.001$) hours after diazepam and two hours after benzhexol ($P<0.02$) compared with placebo (Table 1 and Fig. 2). Caffeine also appeared to impair CFFT at one hour ($P<0.05$). No other drug effects on CFFT could be distinguished from placebo.

Choice reaction time (CRT)

The CRT data yielded a cognitive component (latency or 'recognition movement time'), a motor component ('motor movement time') and a total reaction time. Significant differences between male and female groups meant that each had to be analysed separately for each of the CRT components. The *total CRT* was significantly prolonged in comparison with placebo by benzhexol in both males and females at one and two hours and also by diazepam at these times in females (Table 2). In males, an 18.8% increase in total CRT one hour after diazepam failed to reach a statistically significant difference from placebo ($P<0.2$). Haloperidol (1 mg) was associated with a gradual

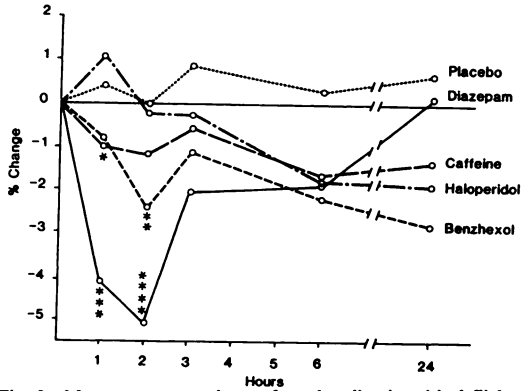

Fig. 2 Mean percentage change from baseline in critical flicker fusion threshold (CFFT) in 20 healthy volunteers (10 males and 10 females). (Difference from placebo: *$P<0.05$, **$P<0.02$, ***$P<0.005$, ****$P<0.001$.)

improvement in total CRT throughout the day, which was statistically significant at three hours in males ($P<0.02$), but not in females.

Caffeine (400 mg) appeared to have opposite effects in the two sexes, being associated with improved performance in females but impairment in males, although none of the differences from placebo were statistically significant. These differences, however, appeared to have been due to the different effects of caffeine on motor speed in each group: *motor movement time* was decreased in the females at one and two hours compared to placebo ($P<0.05$) but showed a gradual but non-significant increase during the day in males (Table 2). The only other statistically significant effect on motor movement time was an increase with benzhexol compared to placebo at six hours in females ($P<0.05$).

There were similar drug effects on CRT latency in the two groups, but although diazepam was associated with significantly prolonged response times at one hour ($P<0.05$) and benztropine at both one ($P<0.005$) and two ($P<0.01$) hours in males, a similar pattern in females did not produce statistically significant differences from placebo (Table 2). Caffeine had no effect on CRT latency in either group.

Automated psychological assessment system (APAS)

The statistically significant results of the APAS, which was only carried out on one occasion on each study day, are shown in Table 3. Compared with placebo, both caffeine ($P<0.02$) and haloperidol ($P<0.05$) were associated with decreases in simple visual reaction times, and benzhexol with an increase in the two-choice reaction time ($P<0.02$) consistent with the Leeds CRT data above. The perceptual maze test (PMT) proved to be relatively insensitive to drug effects, only an impairment of processing speed by benztropine compared with placebo ($P<0.02$) being detected.

Eysenck Personality Questionnaire (EPQ)

To study the effect of personality variables, a multivariate analysis of variance controlling for sex and EPQ subtypes

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Table 3
Automated psychological assessment system (APAS). Mean log-transformed data for total group ($n = 20$)

	Visual reaction time: log m/s	Visual 2-choice reaction time: log m/s	Processing speed: log nodes/s
Placebo	5.592	5.679	6.882
Haloperidol	5.528*	5.693	6.835
Benzhexol	5.650	5.751**	6.699**
Diazepam	5.551	5.658	6.838
Caffeine	5.518**	5.668	6.930

Difference from placebo: *$P<0.05$; **$P<0.02$.

would be desirable. However, with the relatively small numbers in this study this would produce some cells with few or zero numbers. According to EPQ, 14 of the subjects were extraverts and six were introverts; nine were classified as 'stable' and 11 as 'unstable'. There were eight stable extraverts, six unstable extraverts, one stable introvert and five unstable introverts. Comparisons of both raw scores and changes from baseline for the effect of diazepam or benzhexol at one hour on the VARS (alert), CFFT, and CRT data revealed no statistically significant differences between introverts/extraverts or stable/unstable subtypes (Mann–Whitney U). Neither were any differences between extraverts and introverts detected in the baseline CFFT data.

Life events

There were few life events recorded by the subjects and none considered by them to have had a significant effect on their 'state of mind' at the time of any study day.

Discussion

We have demonstrated similar effects of diazepam (10 mg) and benzhexol (5 mg) on subjective alertness, CFFT and psychomotor performance. The effect of benzhexol on CFFT seemed to be less than that of diazepam but persisted longer (Fig. 2). This is also suggested by the fact that benzhexol, but not diazepam, was detected by the APAS at four to five hours post-dose. These findings supplement those of Potamianos & Kellet (1982) who demonstrated impaired memory function in non-demented geriatric patients after 2 mg benzhexol, and are consistent with those reported with hyoscine in human volunteers (Preston *et al*, 1988).

Haloperidol (1 mg), on the other hand, was found to be inactive in most of our tests: the only two significant differences from placebo being in the direction of improved function, i.e. total CRT at three hours in males, and the simple visual reaction time on the APAS (4–5 hours). We also found an early but non-significant increase in CFFT at one hour (Fig. 2). There was, however, no clear trend and these might have been isolated findings. These data are, nevertheless, consistent with the previous suggestions in the literature that, in spite of the unpleasant subjective effects of akathisia and dysphoria, haloperidol can produce improved psychomotor performance in normal volunteers (Janke & Debus, 1972; James & James, 1973; Parrott & Hindmarch, 1975; Saletu *et al*, 1983*a*,*b*). However, a more critical appraisal of these and other studies shows that, in doses of up to 2 mg, haloperidol, although causing increased prolactin levels, is not reliably distinguished from placebo in psychomotor tests (see King, 1990). Indeed, Magliozzi *et al* (1989) found a dose-dependent decrease in DSST using doses of 4 mg and 10 mg and McClelland *et al* (1987, 1990) found 3 mg caused decreased flash fusion threshold at six hours and impaired performance on a rapid information processing task from 4 to 48 hours.

We should also consider whether we used appropriate tests to detect the cognitive effects of neuroleptics. Traditionally the CPT, first used by Mirsky *et al* (1959), has been favoured but later found to produce inconsistent results (Medalia *et al*, 1988). It was thought that it was the paced component of this test which was important (Kornetsky & Orzack, 1964; Broadbent, 1984) as opposed to an unpaced test, such as the DSST, which was more sensitive to barbiturates (Mirsky & Kornetsky, 1964). The PMT of the APAS has a marked cognitive component, is paced (the subjects were prompted after a time limit of two minutes per maze, and were given more difficult mazes and achieved higher scores the faster they worked), and also requires continuous attention. It did not, however, detect haloperidol in our hands. This may have been because it was only administered at one time point (4–5 hours) but this was the expected time of maximum haloperidol effect (Saletu *et al*, 1983*a*,*b*; McClelland *et al*, 1987; Magliozzi *et al*, 1989). Furthermore, an effect of benzhexol on PMT processing speed was detected at this time (Table 3). The effect of haloperidol on the CRT was interesting in that the decrease in total time (in males at 3 hours) was entirely due to a decrease in latency (cognition time) since the motor time was increased (Table 2). (However, a similar dissociation between cognition and motor times did not occur in the female group (Table 2).) This was in contrast to the effects of diazepam and benzhexol which increased both motor and cognition times.

Thus dose, design and choice of test are all relevant in determining whether the effects of haloperidol are detected. What these effects are in healthy volunteers and which are dose-dependent can only be resolved by further studies using a range of doses, at several time points, and more sensitive tests.

Caffeine (400 mg) did not prove to be a successful positive control in most tests, although improved visual reaction time on the APAS (4–5 hours) and motor speed on the CRT at one and two hours (in females) was demonstrated. This may be because discontinuation of caffeine on the day before the study produced a caffeine withdrawal syndrome which can outlast the plasma elimination of caffeine ($t_{½} = 4$ hours) (Bruce & Lader, 1986) which could have either positive or negative effects on performance. Improved performance is notoriously more difficult to detect in well-motivated healthy volunteers, especially with caffeine (Loke & Meliska, 1984), although both Fagan *et al* (1988) and Zwyghuizen-Doorenbos *et al* (1990) have succeeded in doing so using an auditory vigilance test and the Multiple Sleep Latency Test.

Although there were significant group differences between males and females in the CRT data, the patterns of drug effects were similar in both groups with the exception of the haloperidol effect on total CRT (Table 2) and the caffeine effect on motor movement time, which were in opposite directions in males and females. The caffeine difference might be explained by the lower body weight (males 69.5 (11.17) kg, females 59.5 (8.74) kg, $P < 0.04$ (Student's *t*-test)) and/or a lower level of pre-study caffeine use in the females, but there is no obvious explanation for the difference in the effect of haloperidol in the two groups.

The number of subjects was evidently too small to detect an effect of personality variables on drug response in this study. The effects of such variables on drug response seem to be relatively weak and are not evident if the drug effect is marked (Kornetsky & Humphries, 1957) or at higher doses (Barrett & DiMascio, 1966). They have been demonstrated, however, both for benzodiazepines (DiMascio & Barrett, 1965; McDonald, 1967; Nakano *et al*, 1978) and neuroleptics (Heninger *et al*, 1965; Janke & Debus, 1972) in studies which have selected criterion groups on the basis of extreme scores on certain personality traits.

In conclusion, the effects of a commonly prescribed anticholinergic drug, benzhexol, had more persistent effects on subjective alertness and psychomotor function than a low dose of haloperidol, in normal volunteers. Haloperidol appeared to improve performance on some tests but further studies, using multiple doses and better tests of sustained attention, are required to explore further the effects of haloperidol and other non-sedative neuroleptics.

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