Electroencephalographic and psychomotor effects of chlorpromazine and risperidone relative to placebo in normal healthy volunteers

A. M. Hughes, P. Lynch, J. Rhodes, C. M. Ervine & R. A. Yates

Clinical Pharmacology Unit, Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, UK

Aims To investigate the effects of single oral doses of chlorpromazine (50 mg) and risperidone (2 mg) relative to placebo on topographical electroencephalometry (CATEEMTM) and psychomotor tests in 12 healthy male volunteers.

Methods A double-blind, placebo-controlled, three-way crossover design using a double dummy blinding technique was utilized. Chlorpromazine was selected as representative of the 'typical' neuroleptics, being also highly sedative. Risperidone has been suggested as representative of the newer 'atypical' neuroleptics and is claimed to be only minimally sedative. Volunteers were dosed on 3 separate days with a minimum of 7 days interval between trial days. On each trial day volunteers were dosed twice. Dose 1 consisting of either chlorpromazine 50 mg or placebo to chlorpromazine, and dose 2 either risperidone 2 mg or placebo to risperidone. The volunteers were randomized so that each received either chlorpromazine or risperidone (or neither), but not both on an individual trial day. A 17 electrode quantitative topographical electroencephalograph (EEG) recording was taken for each volunteer before and after each dosing period. Seven psychomotor function tests were used to determine the effects of each treatment on psychomotor performance.

Results The data confirm the cited reports of sedation following single oral doses of chlorpromazine 50 mg. However, 7 of the 12 volunteers dosed with risperidone 2 mg also reported drowsiness/lethargy which was of greater severity and duration than 5 of the 12 volunteers who reported somnolence following dosing with chlorpromazine 50 mg. Objective assessment of psychomotor impairment using a short battery of psychomotor function tests mirrored the subjective reports of somnolence in that the impairment in volunteers dosed with risperidone 2 mg was greater in extent and magnitude than in volunteers dosed with chlorpromazine 50 mg. With respect to the cortical quantitative electroencephalogram, both chlorpromazine (50 mg) and risperidone (2 mg) increased power (4.75–6.75 Hz) in keeping with cited effects of other neuroleptics on the quantitative EEG. In addition, there was a statistically significant increase ($P < 0.05$) in α_1 (7.0–9.5 Hz) and β_1 (12.75–18.5 Hz) wavebands in volunteers dosed with risperidone 2 mg. Furthermore, based on estimates of variability, we propose that a 3 min eyes open and 3 min eyes closed quantitative EEG recording is sufficient to maintain adequate power for this technique, whilst allowing its application to early volunteer trials of novel neuroleptic agents.

Conclusions This study demonstrates that quantitative EEG can be utilized in the profiling of neuroleptic agents, and could be readily applied to the early profiling of novel neuroleptics in limited numbers of volunteers, early in drug development. The chosen battery of psychomotor tests has clearly demonstrable sensitivity to the quantification of the subjective reports of somnolence secondary to both chlorpromazine and risperidone.

Keywords: chlorpromazine, EEG, psychomotor function, risperidone

Introduction

Clinically efficacious antipsychotic drugs, are known to have characteristic effects on the quantitative electroencephalogram (EEG) [1–3]. A further characteristic of neuroleptics is that they vary in their side-effect liability including their degree of induced sedation; a feature utilized by prescribers. The purpose of this study was to demonstrate the feasibility of profiling both the activity and side-effect liability of neuroleptics in early drug development with a limited number of volunteers, using computerized topographical EEG and a selected battery of psychomotor function tests, together with an investigation of the optimal duration of EEG capture needed to accurately characterize the quantitative EEG profile. Two comparator neuroleptics were selected; chlorpromazine as representative of the 'typical' neuroleptics, being also highly sedative [4], and risperidone which has been suggested as representative of the newer 'atypical' neuroleptics and is claimed to be only minimally sedative [5]. The doses of each drug were selected as being the highest doses which have been demonstrated to be well tolerated in healthy volunteers [1, 6] and should not be considered as 'dose equivalents' [7].

This trial was designed to confirm that the computer aided topographical electroencephalometry (CATEEMTM) apparatus (Proscience Private Research Institute, Linden, Germany) can detect known effects of neuroleptics on the quantitative EEG. The variability of quantitative EEG power spectra over a 30 min EEG recording, and the effect of opening and closing the eyes on the variability of the quantitative 17 electrode cortical EEG would be used to determine the optimal duration of EEG capture to determine the quantitative EEG profile of chlorpromazine and risperidone. A selected set of psychomotor function tests were profiled as to their ability to quantify subjective reports of sedation, to discriminate between a known sedative neuroleptic (chlorpromazine) and a claimed minimally sedative neuroleptic (risperidone). The psychomotor tests comprised Critical Flicker Fusion (CFF), Choice Reaction Test (CRT), Bond Lader Visual Analogue Scales (B-L VAS), Digit Symbol Substitution Test (DSST), Digit Copying Test (DCT), Number Cancellation Test (NCT) and Finger Tapping (FT).

Methods

Ethical considerations

The study protocol was approved by Zeneca Pharmaceuticals independent research ethics committee. All volunteers gave their written informed consent following a verbal explanation of the study and after reading a detailed information sheet.

Design

This trial was double-blind, randomised, and placebo-controlled. It utilized a three-period crossover design to assess the effect of chlorpromazine 50 mg and risperidone 2 mg on the quantitative EEG and a selected set of psychomotor function tests in healthy male volunteers relative to placebo. There was a minimum of 1 week washout between each of the three treatment periods. The EEG and psychomotor tests were performed at the anticipated time of maximum serum concentrations (t_{max}) of the chosen neuroleptics.

Subjects

The trial was conducted in 12 healthy male Caucasian volunteers (including 7 nonsmokers) aged 18–43 years (mean 30.8 years), of weight 64–92 kg (mean 78.3 kg) and height 171–189 cm (mean 178.1 cm). Each subject was required to have a normal clinical examination including medical history, electrocardiogram (ECG) and 24 h continuous ambulatory ECG, a cortical quantitative EEG without evidence of spike and wave activity (5 min eyes open; 5 min eyes closed recording) and clinical chemistry, haematology and urinalysis within the laboratory reference ranges. In order to reduce data variability the protocolled inclusion and exclusion criteria ensured a controlled population. Subjects were not to have participated in drug studies within 3 months of the start of the present study. Volunteers were requested to stop smoking and taking caffeine containing drinks or food and alcohol for at least 12 h before each experimental session. Volunteers were also required to be in bed by 23.00 h on the night before each trial day. Volunteers reported to the Clinical Pharmacology Unit (CPU) at Zeneca Pharmaceuticals after an overnight fast from midnight of the day before. All subjects indicated compliance with these requests.

Drugs, dose and administration

All drugs were supplied as tablets containing either chlorpromazine (LargactilTM; Rhone-Poulenc Rorer Ltd),

Correspondence: Dr A. M. Hughes, Clinical Pharmacology Unit, Astra Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield SK10 4TG, Cheshire, UK.

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risperidone (RisperdalTM: Janssen-Cilag Ltd) or matching placebo (Zeneca Pharmaceuticals Ltd) for oral use. Tablet strength of chlorpromazine and risperidone were supplied as 50 mg and 2 mg, respectively. The $t_{\max}$ and half-life of chlorpromazine is 2–4 h and 15–30 h, respectively [4, 8], the corresponding values for risperidone being 1–2 h and 24 h, respectively [Lucker & Becker, unpublished results]. This required a double dummy design and two dosing occasions to allow one postdose assessment to correspond to the varying $t_{\max}$ of both comparator neuroleptics. Dose 1 consisted of either 50 mg chlorpromazine or placebo to chlorpromazine administered 3 h before pharmacodynamic assessments and dose 2 was either 2 mg risperidone or placebo to risperidone administered 1.5 h before pharmacodynamic assessments; volunteers were randomized so that each volunteer received either chlorpromazine or risperidone (or neither) but not both on an individual trial day.

Quantitative electroencephalography

On each trial day each volunteer's quantitative EEG was recorded twice; once for 30 min predose and once for 30 min, 3 h after dosing with chlorpromazine or placebo to chlorpromazine (1 h 30 min after dosing with risperidone or placebo to risperidone). All recordings took place in a quietened ward environment with the curtains drawn around the bed.

On the morning of each trial day the volunteers attended the CPU having been asked to wash their hair, and were fitted with an electrode cap approximately 30 min before the predose EEG recording. The electrode cap consisted of a shaped cloth cap on which 17 hollow metal electrodes are positioned according to the international 10:20 system [9]. These electrodes were back filled with electrode jelly prior to placing the cap on the head. The cap was positioned so that the front and back are equidistant from the nasion and equidistant from the ears. Electrical contact with the scalp was made by top filling the electrodes with electrode jelly until the volunteer felt the jelly on the scalp. The size of electrode cap worn by each volunteer was recorded to ensure that the same size was used on each trial day. As part of the artefact rejection procedure, an electrooculogram electrode was placed on the temple, and ECG electrodes were strapped to the wrists. Micro-voltage potentials recorded from each of the 17 scalp electrodes were displayed continuously on a video monitor. The analogue signals were processed by the CATEEMTM computer to provide power spectra for each recording session at each of the following frequency bands:-

Band	Frequency (Hz)
δ	1.25–4.50
θ	4.75–6.75
α_1	7.0–9.50
α_2	9.75–12.50
β_1	12.75–18.50
β_2	18.75–35.00

During each 30 min EEG recording session, the volunteers had their eyes open (viewing a screensaver computer programme) and closed for certain periods of time as follows:-

Time period (min)	Eyes
0–2	Open
2–5	Closed
5–20	Open
20–30	Closed

The amount of activity in each frequency band was taken to be the power in that frequency band, summed across the 17 electrodes. The power in each frequency band was calculated for eyes open and eyes closed data separately. Total power is the cumulative power summed across all frequency bands. It was decided prospectively that only data which was artefact free for $\geq 30\%$ of the recording duration was used in the subsequent summary and analysis.

Psychomotor function tests

Seven psychomotor tests were used to determine the effects of each treatment on cognitive function. The tests were:

Critical Flicker Fusion (CFF) This utilized a commercially available apparatus (Human Psychopharmacology Research Unit, University of Surrey, UK) in which a flickering red light source (rectangle of 4 light-emitting diodes) was placed 1 metre from the eyes and was presented at alternating ascending and descending frequencies. The frequency at which a flickering light source could no longer be perceived (for ascending frequencies) or was first perceived to be flickering (for descending frequencies) by the volunteer was identified. The mean of the three ascending and three descending frequency presentations was recorded in Hz.

Choice Reaction Test (CRT) This utilized a commercially available apparatus (Human Psychopharmacology Research Unit, University of Surrey UK) in which a

volunteer was required to extinguish one of six red stimulus lights by touching a nearby response pad. One of the red stimulus lights was triggered to illuminate after a random delay of 1–5 s, returning the index finger to the central start pad completed the sequence. Reaction times in milliseconds were taken as the time to remove the finger from the starting pad (recognition reaction time; RRT), the time to reach the stimulus light pad (motor reaction time; MRT), and the sum of both (total reaction time; TRT).

Bond-Lader Visual Analogue Scales (B-L VAS) volunteers were asked to mark 16 visual analogue scales on a computer screen. From these 16 scales three factors were derived which measured 'alertness', 'contentedness' and 'calmness' according to the method of Bond & Lader [10].

Digit Symbol Substitution Test (DSST) This was a paper and pencil test in which each volunteer was presented with a code equating symbols with numbers. A random sequence of numbers was then displayed, and each volunteer was required to match each number with its correct symbol. The score depended on the number of correctly and incorrectly coded symbols completed in 90 s.

Number Cancellation Test (NCT) Volunteers were required using a pencil on paper to delete all the number '4's in a randomised array of 400 digits from 0 to 9, including a total of 40 number 4s. The score is the time taken to complete the test (seconds).

Digit Copying Test (DCT) This was a paper and pencil test in which volunteers had to copy a variety of symbols highlighted in a box above into the space provided. The score is the number of correct and incorrect copyings completed within 90 s.

Finger Tapping (FT) the volunteer was asked to tap a computer key as quickly as possible for 30 s using the middle finger of the dominant hand. The variable derived was the number of taps completed in the middle 20 s of the assessment period, and expressed as the number of taps per minute.

A standard set of instructions was presented to each volunteer prior to each test. All assessments were done in a quiet room with overhead fluorescent lighting, but no windows.

Each volunteer attended the CPU on two occasions approximately 14 days and 7 days prior to the start of the trial. On each occasion, CPU personnel trained in these tests instructed the volunteer using standard wording on how to perform the test battery. Immediately following the instruction, each volunteer performed the tests twice under direct supervision and standard conditions.

On each trial day the set of psychomotor tests were performed under direct supervision with standard verbal instructions prior to each test battery, once predose and then once 3 h 30 min after dosing with chlorpromazine or placebo to chlorpromazine (2 h after dosing with risperidone or placebo to risperidone).

There were five versions of each of the three paper tests (DSST, NCT and DCT). Two versions were used during the pretrial familiarization sessions, each being used once on each of the two 'training' days. The remaining three versions of each test were used twice during the 3 trial days, with a minimum of 7 days between each use. At each session, the seven psychomotor tests were presented in the order CFF, FT, CRT, NCT, DCT, DSST, B-L VAS. Randomization of treatment sequences precluded the need to randomise the different versions of the tests.

Adverse event monitoring

Any symptoms the volunteers experienced were recorded by the volunteer at 1 h 45 min before dosing and at 1 h, 1 h 30 min, 2 h 30 min, 4 h, 6 h and 8 h after dose 1 on each trial day. The investigator subsequently coded the maximum severity, time of onset and duration, seriousness and whether treatment was required, together with a blinded assessment of causality to trial medication.

Endpoints and methods of analysis

In the analysis of the EEG power spectra, the log transformed total power for each frequency band and overall total power was analysed using an analysis of covariance, fitting for the effects of volunteers, treatments and periods, with the predose measurement as a covariate. This analysis was performed for time intervals 0–2 min (eyes open) and 2–5 min (eyes closed). Comparisons were made between each of the active treatments and placebo. The effect of carry-over was assessed by creating a dummy variable which took the value of the placebo treatment in the first period, and the treatment in the previous period for periods 2 and 3. The same analysis was used to analyse the cumulative total power for each frequency band and overall power, for eyes open and eyes closed data separately. The assumptions of normality were checked when applying the above models by using probability plots.

In the analysis of the EEG data, the results were back transformed and have been presented in terms of percentage change in adjusted geometric means (glsmens). The percentage change in glsmens was calculated directly by taking the antilog of the difference in lsmeans, subtracting 1 and then multiplying by 100 i.e.

$$\{[\text{Anti-log}(\text{difference in lsmean})] - 1\} \times 100$$

Histograms of the percentage change in glsmeans for eyes open (0–2 min) and eyes closed (2–5 min) for each waveband have been produced in Figure 1 and 2, respectively.

The residual standard deviation from the analysis of the cumulative power for eyes open and eyes closed data has been presented graphically in Figure 3, for eyes open and eyes closed data for overall power.

The endpoints for analysis of the psychomotor tests were as follows:

DSST number correct **

DCT number correct **

NCT number of 4s deleted**

time taken

FTT number of taps min^{-1}

B-L VAS alert factor contentedness factor calm factor

CFFT overall mean frequency

CRT mean and median recognition response time
mean and median motor response time mean and median total response time

**discrete data

For the continuous data, an analysis of covariance model was used, fitting for the effects of volunteers, treatments and periods, with the predose measurement being used as a covariate. Comparisons were made between each of the active treatments and placebo, and between the two active treatments. The effect of carry-over was assessed as described in the analysis of EEG section, as were the assumptions of normality using probability plots.

For the CRT, comparisons of the standard error of the treatment effect between mean measurements and median measurements were made to evaluate which measurement was the most appropriate endpoint for use in future trials.

For the discrete data, an analysis of covariance model was not appropriate as these data did not conform to a

Figure 1 Histogram showing percentage change in adjusted geometric mean power relative to placebo for EEG power spectra (microvolts^2) for eyes open data (0–2 min).

Figure 2 Histogram showing percentage change in adjusted geometric mean power relative to placebo for EEG power spectra (microvolts^2) for eyes closed data (2–5 min).

Figure 3 Residual standard deviation in variability of total power over time during periods of eyes open (■) and eyes closed (□).

normal distribution. These data fell within a tight range and had a physical minimum and maximum value. They were therefore analysed using the non parametric Wilcoxon signed rank test. Pair wise comparisons were made between each of the active treatments and placebo, and between the two active treatments.

In the analysis of the continuous psychomotor function tests data, the results have been presented in terms of least square means (lsmeans) for each of the active treatments and placebo, % difference in lsmeans together with the associated 95% confidence intervals. The percentage difference in lsmeans was calculated by

dividing the difference in lsmeans by the lsmean of the second comparison treatment, and then multiplying by 100. For example, if the comparison of interest was between chlorpromazine and placebo, the percentage difference was calculated as:

$$\{[\text{difference in lsmeans}]/\text{placebo lsmean} \times 100\}$$

The confidence limits for the percentage difference were calculated similarly.

In the analysis of the discrete psychomotor data, the results have been presented in terms of median change from predose, treatment effect (being the median difference between treatments) and *P* value.

Results

Effects of chlorpromazine 50 mg and risperidone 2 mg on the quantitative EEG

In the θ , α_1 and β_1 frequency bands, there was a statistically significant increase at the conventional 5% level ($P \leq 0.05$) in mean total power in volunteers dosed with risperidone 2 mg compared to placebo of 21% (CI 6–39%), 25% (CI 6–48%) and 16% (CI 2–32%), respectively (Figure 1). Also in the θ frequency band, an increase by 16% (CI 1–33%) in mean total power in volunteers receiving chlorpromazine 50 mg with respect to placebo was found.

In the analysis the first 3 min of eyes closed recording, a statistically significant increase at the conventional 5% significance level in mean total power was found in volunteers receiving risperidone 2 mg compared with placebo in the α and wavebands by 13% (CI 0–28%) and 47% (CI 16–85%), respectively (Figure 2). No statistically significant effects on the quantitative EEG were observed following dosing with chlorpromazine 50 mg with eyes closed for any of the wavebands.

Assessment of the variability of quantitative EEG using CATEEMTM over time and with opening and closing of eyes

Variability of 17 electrode cortical quantitative EEG data appears lower during periods when volunteers have their eyes closed than when they have eyes open and viewing a screensaver (Figure 3). It is also apparent that little advantage in reduced variability is conferred by prolonging the duration of recording for either eyes open or eyes closed. Thus the variability of data during the second eyes open period of 15 min is similar to that of the initial 2 min eyes open recording period. Also, the variability of data during the second eyes closed recording period of 10 min is similar to that of the initial 3 min eyes closed period. As such, a 3 min sampling time of the cortical EEG would appear to provide an optimal balance

between ease of use and precision of data capture. The variability of the technique is such that for a trial utilizing a three period crossover design, a total of 12 volunteers is sufficient to detect a treatment difference of 30% with a least 95% power in the analysis of EEG data with eyes open.

The effects of chlorpromazine 50 mg and risperidone 2 mg on psychomotor function tests

The effect of chlorpromazine 50 mg (CPZ) and risperidone 2 mg (RIS) on a set of psychomotor function tests is shown in Table 1.

At 1.5 h after dosing with risperidone 2 mg, volunteers psychomotor performance was statistically significantly impaired with respect to placebo as assessed by number cancellation test, finger tapping test, choice reaction test (recognition, motor and total reaction time) critical flicker fusion, and Bond-Lader visual analogue scales (alertness and contentedness factor). Whilst there was some impairment of psychomotor function 3 h after dosing volunteers with chlorpromazine 50 mg with respect to placebo, this was less evident in the extent (only choice reaction time [recognition, motor and total reaction time], digit symbol substitution test and Bond-Lader VAS [alertness]) of psychomotor tests which demonstrated a statistically significant impairment with respect to placebo and in the magnitude of the change. The greater sedative potential of risperidone 2 mg than chlorpromazine 50 mg in healthy male volunteers is further endorsed in that for number cancellation test, finger tapping test, digit copying test and Bond-Lader VAS (alertness) there was a statistically significant impairment of psychomotor function in volunteers dosed with risperidone 2 mg with respect to chlorpromazine 50 mg.

Effect of chlorpromazine (50 mg) and risperidone (2 mg) on adverse event reports of somnolence

The trial was able to assess qualitatively the sedative properties of chlorpromazine 50 mg and risperidone 2 mg from adverse event monitoring. There were six reports (four mild and two moderate) of drowsiness/lethargy from 5 of the 12 volunteers receiving 50 mg chlorpromazine in keeping with the sedative properties of chlorpromazine, and occurred typically 1–2 h following dosing (minimum 59 min, maximum 6 h 30 min) which is in keeping with the known $t_{\max}$ of chlorpromazine 2–3 h. The mean duration of reported drowsiness was some 4 h 18 min (minimum 1 h 32 min, maximum 13 h) in keeping with the cited reports on the duration of sedation following 50 mg chlorpromazine in healthy volunteers [1]. The investigator considered all six of the events to be probably related to trial medication. More surprisingly

Table 1 Effects of chlorpromazine and risperidone on psychomotor function tests.

Test	Placebo	CPZ	RIS	RIS vs Placebo	Treatment effect: Mean (CI)	
	LS mean ($\pm$ s.d.)	LS mean ($\pm$ s.d.)	LS mean ($\pm$ s.d.)		CPZ vs Placebo	CPZ vs RIS
NCT (mean s)	53.2 (11.1)	55.0 (12.3)	57.6 (14.4)	8.3%* (3.7, 13.0)	3.5% (−1.2, 8.2)	−4.5%* (−8.3, −0.1)
FT (mean number)	370.3 (32.2)	363.1 (37.5)	351.4 (25.5)	−5.1%* (−8.0, −2.2)	−1.9% (−4.6, 0.8)	3.3%* (0.3, 6.3)
CRT-RRT (median ms)	321.2 (28.8)	336.3 (29.9)	347.2 (29.1)	8.1%* (4.1, 12.0)	4.7%* (1.0, 8.4)	−3.1% (−6.6, 0.3)
CRT-MRT (median ms)	240.3 (52.5)	267.4 (61.4)	265.3 (53.1)	10.4%* (4.1, 16.7)	11.3%* (4.7, 17.8)	0.8% (−5.7, 7.3)
CRT-TRT (median ms)	574.2 (70.1)	605.2 (75.5)	626.0 (89.8)	9.0%* (4.7, 13.3)	5.4%* (0.9, 9.9)	−3.3% (−7.4, 0.8)
CFF (mean Hz)	32.7 (3.8)	31.8 (4.2)	31.0 (3.9)	−5.2%* (−8.2, −2.2)	−2.7% (−6.1, 0.7)	2.6% (−0.5, 5.8)
B-L VAS (alert factor)	434.7 (114.2)	382.2 (130.0)	336.0 (136.6)	−22.7%* (−33.3, −12.1)	−12.1%* (−22.6, −1.5)	13.8%* (0.1, 27.5)
B-L VAS (contented factor)	272.1 (55.1)	264.6 (56.7)	250.4 (66.9)	−8.0%* (−14.6, −1.3)	−2.8% (−9.5, 4.0)	5.7% (−1.6, 12.9)
B-L VAS (calm factor)	101.5 (25.8)	116.0 (25.2)	108.9 (20.8)	7.3% (−3.6, 18.2)	14.4% (3.8, 24.9)	6.6% (−2.8, 15.9)
DSST (median change)	4.0	−2.5	−3.0	−6.5 ⁺ #	−5.5 [#]	0.5 [#]
DCT (median change)	3.0	1.0	−9.0	−7.5 ⁺ #	−2.0 [#]	9.0 ⁺ #

* = Statistically significant at $P \leq 0.05$ using ANCOVA. + = Statistically significant at $P \leq 0.05$ using the non parametric Wilcoxon signed rank test.
 # = Treatment effect is median difference between treatments.

7 of the 12 volunteers dosed with 2 mg risperidone reported 8 episodes of drowsiness/lethargy (4 mild, 3 moderate and 1 severe in maximum intensity). The onset of sedation was typically 2–3 h (minimum 1 h, maximum 6.3 h) post risperidone, in keeping with the known $t_{\max}$ of 1–2 h, and had a mean duration of 8 h (minimum 1 h, maximum 27 h). The investigator considered all eight of the episodes to be probably related to trial medication.

Discussion

This trial has demonstrated that the computerized topographical CATEEMTM EEG equipment can detect changes in the cortical quantitative EEG frequency band power produced by two neuroleptics compared with placebo. As such it appears a suitable tool in screening for CNS activity of novel antipsychotic agents in healthy volunteers.

For both risperidone and chlorpromazine the effects on the different wavebands of the EEG are like those produced by other neuroleptic drugs [1, 8] and distinct from that produced by other classes of centrally active drugs (Table 2).

This may aid the selection of effective neuroleptics drugs in early drug development trials in man by looking for the specific EEG 'fingerprint' of neuroleptics. The increase in alpha and beta power following risperidone, has been previously reported for risperidone in schizophrenic subjects [12] and haloperidol in healthy volunteers [13]. The increase in beta power with risperidone has suggested to correlate with clinical response [13], with increases in alpha power also suggested as being a principal EEG correlate for favourable clinical response in schizo-

Table 2 Effects of CNS active drugs on the quantitative EEG

Drug class	Wave band					
	δ	θ	α_1	α_2	β_1	β_2
Benzodiazepines	Ø	↓	↓	↓	↑	↑
Theophylline	Ø	↓	↓	↓	↓	Ø
Ethanol	↑	↑	↑	↓	Ø	Ø
Neuroleptics	↑	↑	↓	↓	↓	Ø

Ø = Uncharacteristic

(Data summarized from references 1, 2, 3, 8 and 11)

phrenic patients [6] The increase in delta range after neuroleptic administration is generally observed when subjects are heavily sedated [14].

Based on estimates of variability, we propose that a 3 min eyes open, 3 min eyes closed quantitative EEG recording is sufficient to maintain adequate power for this technique, whilst allowing its easy utilization in early volunteer trials of novel neuroleptic agents.

This battery of psychomotor function tests allowed us to assess quantitatively the magnitude of the psychomotor function impairment produced by risperidone 2 mg and chlorpromazine 50 mg. Objective quantitative measurement of sedation using psychomotor function tests demonstrated, that contrary to our expectations, the impairment of psychomotor performance was significantly greater in magnitude and extent (both clinically and statistically) after volunteers received risperidone 2 mg than after chlorpromazine 50 mg. This finding was reinforced by the subjective reporting of drowsiness/lethargy which was more frequently and with

greater severity and duration reported in volunteers dosed with risperidone 2 mg than chlorpromazine 50 mg. Although this study did clearly demonstrate that the selected battery of psychomotor function tests were able to quantify and correlate volunteers subjective reports of greater somnolence following a 2 mg oral dose of risperidone than a 50-mg oral dose of chlorpromazine, the data do not support conclusions as to the relative potential of these agents to produce somnolence in clinical practice. It has been shown that the quietened ward environment of volunteer investigational units are of themselves a somnolent environment, over-exaggerating the sedative liability of the investigational product [15]. In addition, the clinically utilized dose of chlorpromazine is typically 2–8 fold that used in this study, whereas the 2 mg risperidone dose more closely approximates its clinically effective antipsychotic dose [5]. Furthermore, it is not uncommon for tolerance to develop to somnolence on multiple dosing, such that single dose studies such as this, are severely limited in determining sedative liability on chronic dosing in clinical practice. Indeed, atypical antipsychotics including risperidone may improve cognitive functioning in schizophrenic patients relative to the typical antipsychotics such as chlorpromazine [16, 17]. Finally, 2 mg Risperidone and 50 mg Chlorpromazine should not be considered as necessarily 'dose equivalents'. In volunteers, a PET study has indicated risperidone to occupy 40–55% of basal ganglia D₂ receptors at a dose of 1 mg [18] whereas a dose of some 150 mg chlorpromazine is required to achieve similar PET receptor occupancy [19, 20].

This study provides a feasible method for the early profiling of activity and side-effect liability of novel antipsychotic agents, using quantitative computerized EEG and psychomotor function testing in the same subject. As our understanding of the clinical correlates of quantitative EEG changes improve, clinical profiling of the efficacy profiling of antipsychotic agents using quantitative EEG, may become possible.

Conflict of interest statement: All authors are employed by Zeneca Pharmaceuticals, who market the atypical antipsychotic agent, SeroquelTM, for the treatment of schizophrenia.

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