Central effects of the diuretic, bendrofluazide

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1 Central effects of the diuretic, bendrofluazide (2.5, 5 and 10 mg) were studied in 12 healthy volunteers. Two placebos and an active control drug, oxazepam (15 mg), were included. Single doses were administered double-blind at 10.00 h. The effects of drugs on performance and subjective feelings were assessed before and from 1.5–2.5 and 3.5–4.5 h after ingestion, and recordings of the electrical activity of the brain (EEG) and body sway carried out.

2 Performance was assessed using digit symbol substitution, continuous attention, letter cancellation, choice reaction time, finger tapping, immediate and short-term memory, together with critical flicker fusion and two flash fusion. Subjects assessed their mood and well-being on a series of 12 visual analogue scales. The EEG was recorded with eyes open while the subjects carried out a mental arithmetic task, and with eyes closed, when they were required to relax. Body sway was recorded with eyes open and with eyes closed.

3 Bendrofluazide (10 mg) increased the number of errors at letter cancellation and reduced the rate of finger tapping \( P < 0.05 \), while oxazepam increased the number of errors and reduced accuracy at continuous attention \( P < 0.01 \), and increased the number of involuntary rest pauses during tapping \( P < 0.05 \).

4 There were no effects of drugs on subjective assessment of mood.

5 No changes in the electrical activity of the brain were observed with bendrofluazide. In recordings with eyes open, oxazepam reduced delta (0.5–3 Hz), theta (3.5–7 Hz) and alpha 2 (10.5–13 Hz) while increasing beta 1 (13.5–21 Hz) activity. With eyes closed, oxazepam decreased alpha 1 (7.5–10 Hz) and alpha 2 power. These changes were statistically significant at the 5% level or less.

6 Bendrofluazide (2.5 mg) increased the amplitude of body sway in the frequency range 0.05–1.0 Hz \( P < 0.05 \), while oxazepam increased activity in ranges 0.05–1.0 Hz \( P < 0.01 \) and 3.25–4.0 Hz \( P < 0.05 \).

7 There was no evidence for any central effect of the diuretic, bendrofluazide, although adverse changes in psychomotor performance and body sway were apparent. Despite the absence of sedation or reduced vigilance, the effects on performance suggest that diuretics may not be the most appropriate medication for individuals engaged in skilled activity, given the availability of alternative medications such as angiotensin converting enzyme inhibitors that do not impair performance.

**Keywords** bendrofluazide diuretic performance CNS effects

**Introduction**

Mild hypertension affects a significant proportion of the working population, and there is now a wide range of drugs available for treatment. However the incidence and nature of unacceptable side effects varies greatly between classes of drug, particularly those that are related to changes in the central nervous system. This issue is important, particularly for those individuals engaged in skilled employment. Previously we have
investigated the major classes of antihypertensive drugs using a comprehensive and standardised range of performance tests and measures of central activity to identify treatments with least adverse effects. Sedation and reduced vigilance were evident with the β-adrenoceptor antagonists, propranolol and atenolol [1, 2], while captopril, an angiotensin converting enzyme inhibitor, did not adversely affect central function [3, 4]. The calcium antagonist, nifedipine, modified activity of the central nervous system, although alertness and performance were unaffected [5]. The present study now assesses the central effects of a thiazide diuretic, bendrofluazide, which despite its frequent use particularly in combination with other antihypertensive drugs has not been systematically investigated with regard to changes in central function.

Methods

Subjects and restrictions

The subjects were 12 healthy male volunteers aged between 21 and 35 (mean 26.2) years, weighing between 66 and 97 (mean 74.5) kg, and were students or university employees. The study was approved by the Hospital Ethics Committee, and subjects were required to provide written informed consent. Individuals with a history of asthma, insulin dependent diabetes mellitus or hypertension were excluded from the trial. Similarly, those receiving treatment with sedative, hypnotic, antidepressant or antihypertensive medication were excluded.

During the study, subjects were asked to abstain from alcohol on the evening before each experiment and to retire at their usual bed-time. They were asked to eat a light breakfast before attending the laboratory, and upon arrival were screened to ensure that no alcohol had been consumed. No caffeine-containing beverages were allowed during the day of the study.

Each subject ingested single doses of bendrofluazide (2.5, 5 or 10 mg), and two inactive placebos and an active control drug, oxazepam (15 mg), were included in the study. The drugs were administered double-blind according to a multiple Latin square design, with one placebo included in each half of the design. Treatments were separated by at least 1 week. The drugs were taken orally at 11.00 h, and performance and physiological parameters tested 1 h before (10.00 h) and from 1.5–2.5 h and from 3.5–4.5 h after ingestion. Heart rate and resting blood pressure were recorded during each session. Venous blood was taken during the two post-ingestion sessions, and the samples spun and stored at −20°C until analysis. Plasma bendrofluazide concentrations were evaluated by high-performance liquid chromatography [6].

Performance testing and physiological procedures

Before the study began, subjects were trained to plateau level on each of the performance tests and were familiarised with the schedule and physiological procedures. On days of the study, each test session lasted approximately 1 h and consisted of several aspects of performance, critical flicker fusion and two-flash fusion, subjective assessment of well-being and recordings of body sway and the waking electroencephalogram (EEG).

Performance and the EEG were recorded in individual cubicles, and critical flicker fusion and two-flash fusion tested in a room with controlled lighting to allow dark adaptation. All measures other than memory were completed on three occasions each day.

Digit symbol substitution test (DSST) Two sheets each containing 200 randomised digits and a code relating each digit to a symbol were presented to the subjects. For each sheet, they were given 2 min to complete as many substitutions as possible, and the total number of substitutions recorded.

Six-letter cancellation Subjects were presented with a single sheet containing 1200 randomised letters arranged in 40 columns, with 6 target letters printed at the top. They were required to cancel as many target letters as possible in 5 min, and the number of letters correctly cancelled, attempted and errors were recorded.

Continuous attention A randomised series of letters generated by microcomputer was presented on individual TV monitors at a rate of one per second, and a ‘critical stimulus’ consisting of two letters displayed continuously on the screen. Subjects were required to press a key within 750 ms when the second letter followed the first in the random series. The test lasted 15 min, and the number of correct responses and errors were recorded.

Choice reaction time (CRT) Subjects pressed a key corresponding to one of four light emitting diodes illuminated in a random sequence of 30 presentations. Mean reaction time to the last 20 responses was measured.

Short term memory Immediately before drug ingestion, the subjects were presented with a set of twelve photographs of unrelated objects and given 1 min to memorise them. Four hours after drug ingestion they were allowed 45 s to recall and write down as many objects as possible.

Immediate and delayed recall memory Two hours after ingestion, immediate recall was tested by presenting a list of 16 unrelated words (two syllable nouns). These were generated by microcomputer and displayed on TV monitors at a rate of one word every 3 s. Immediately after the presentations subjects were allowed 45 s to write down all words recalled. In addition, the subjects were required to recall the word lists 2 h later, corresponding to 4 h after drug ingestion (denoted ‘delayed recall’ in Results section and Table 1).
**Finger tapping** Subjects tapped a pressure-sensitive transducer as rapidly as possible for 1 min, and the total number of taps and involuntary rest pauses exceeding 250 ms were recorded.

**Critical flicker fusion** Flicker fusion threshold was measured using a central flickering source, with the initial frequency chosen randomly between 15 and 20 Hz. Frequency then increased or decreased by 4 Hz depending on whether the subject perceived a flickering or fused source. Subsequent changes in response halved the step size until steps of 0.25 Hz were reached. Each stimulus was presented for 2 s and fusion threshold defined as a mean of the last 20 presentations of step size 0.25 Hz.

**Two-flash fusion** Pairs of 10 ms flashes of light separated by a period between 12 and 120 ms were presented, and the subjects required to report whether the light sources appeared as two separate flashes or were fused. Initial separation was between 50 and 63 ms, with subsequent increases or decreases of 8 ms depending on the subject’s response. The step size was then halved until steps of 1 ms were reached. Flash fusion point was defined as a mean of the last 20 responses of 1 ms step size.

**Subjective assessments** Subjects assessed their mood and well-being on a series of twelve 100 mm visual analogue scales (0–100) presented on a single sheet, with scores toward 100 representing favourable subjective feelings. The assessments were: A: I am, extremely sleepy (0) – extremely wide awake (100); B: I am, extremely tense (0) – absolutely relaxed (100); C: I am, extremely agitated (0) – absolutely calm (100); D: I am, extremely lethargic (0) – extremely energetic (100); E: I am, mentally very dull (0) – extremely alert (100); F: I have, no ability to concentrate (0) – complete ability to concentrate (100); G: with regard to carrying out general duties I feel that I am, absolutely useless (0) – extremely efficient (100); H: I am, extremely irritable (0) – not at all irritable (100); I: I am extremely aggressive (0) – extremely passive (100); J: I feel, extremely withdrawn (0) – extremely sociable (100); K: I am, in the depths of depression (0) – ecstatically happy (100); L: I feel, extremely anxious (0) – absolutely carefree (100).

**Electroencephalograms**

Waking activity was recorded from P3–O1 and C3–T3 (10–20 international system), using silver-silver chloride electrodes with inter-electrode resistance less than 10 kΩ. The EEG was recorded for 1 min with eyes open while the subjects performed a mental arithmetic task, and this was followed by recording 5 min with eyes closed, when the subjects were instructed to relax. The signals were recorded on magnetic cassettes (TDK 60) using ambulatory four-channel Medilog recorders (Oxford Medilog Systems, Model 4–24).

The tapes were replayed at 20 times real-time using a Medilog Page Mode Display (PMD-12) controlled by a Microvax II computer. The analogue data were low pass filtered before digitisation at a sampling rate of 2560 Hz (equivalent to 128 Hz real-time). Epochs containing artefacts were identified and excluded from subsequent analysis. From each recording with eyes open, fifteen epochs of 4 s duration were analysed, and power spectra (0.25 Hz resolution) for each epoch were computed using a fast Fourier transform. A mean power spectrum based on fifteen epochs (1 min of data) was then calculated. Sixty epochs of 4 s were analysed from each recording with eyes closed, and four mean power spectra (0.25 Hz resolution) relating to consecutive intervals of 1 min calculated. From each mean spectrum (one eyes open, four eyes closed), the total power in six bands (delta: 0.5–3 Hz, theta 3.5–7.0 Hz, alpha 1: 7.5–10 Hz, alpha 2: 10.5–13 Hz, beta 1: 13.5–21 Hz, beta 2: 21.5–30 Hz) were computed. Total alpha power (7.5–13 Hz) and total power (0.5–3.0 Hz) were also calculated.

**Body sway**

The subjects stood on a rigid platform which rested on three pressure transducers (one at the front, two at the back), providing measurement of lateral and anterior body sway. Data were recorded for 1 min with eyes open and then with eyes closed. For each recording, a period of 32 s was digitised off-line at a sampling rate of 32 Hz. A mean power spectrum with resolution of 0.25 Hz over the frequency range 0.05–4 Hz was computed using a fast Fourier transform. Spectra from lateral and posterior channels were summed to give a single mean spectrum for each condition, which was subsequently represented as four bands of 1 Hz bin width.

**Statistical analysis**

All data were analysed using analysis of variance (ANOVA), with the factors drugs, times and subjects specified in the model. Drugs and times were fixed effects and subjects a random effect. The assumptions of ANOVA – homogeneity of variance, normality and independence – were examined for each variable, and transformations of the data selected where appropriate using the method of maximum likelihood of Box & Cox [7].

The pre-ingestion sessions were screened for homogeneity, and where no differences were found direct comparisons of mean drug and placebo values after ingestion were made. Where differences at pre-ingestion time occurred, changes from pre-ingestion level were used to compare drug responses with placebo at each post-ingestion time. Based on this criterion, direct comparisons of drugs with placebo were made for all measures other than the EEG, where changes from pre-ingestion time for the drug and placebo treatments were compared.

Single doses of bendrofluazide and the mean response over dose, together with oxazepam were
compared with the mean of the two placebos at 2 and 4 h after ingestion, and the response of each drug meaned over post-ingestion sessions estimated. Significance levels for all comparisons were adjusted to allow for multiple simultaneous comparisons using the appropriate Bonferroni bound [8], and Dunnett’s procedure [9].

Principal components analysis was used to analyse mood assessments, and component scores tested for drug effects using ANOVA and subsequent individual comparisons. Individual assessments were examined but are reported only where additional explanation of effects is provided.

Results

Performance tests

The findings are shown in Table 1. Bendrofluazide (10 mg) increased the number of errors (P < 0.05) during cancellation 4 h after drug ingestion, while at the same time the number of taps was reduced by bendrofluazide meaned over dose (P < 0.05). Oxazepam (15 mg) increased the number of errors and reduced accuracy at continuous attention 2 and 4 h after ingestion (P < 0.05) and when post-ingestion sessions were meaned (P < 0.01). Additionally, the number of involuntary rest pauses increased (P < 0.05) during the tapping task 2 h after ingestion and when both sessions were meaned.

Subjective assessments

Four principal components derived from the 12 assessments explained 72% of the variance. The first component, representing assessments A, D, E, F, G and J, reflected alertness. The remaining three components represented scales B, C and L; scale K; and scales H and I and were related to aspects of mood attributed to agitation, depression and aggression respectively.

The loadings on principal components for each drug are shown in Table 2. No effects of drugs were observed on any of the principal components or individual mood assessments.

Table 1 Effects of bendrofluazide on performance (means for 12 subjects)

<table>
<thead>
<tr>
<th></th>
<th>Time after ingestion (h)</th>
<th>Placebo</th>
<th>Oxazepam 15 mg</th>
<th>Bendrofluazide (mg)</th>
<th>Mean</th>
<th>Standard error</th>
<th>Transform</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSST</td>
<td>Mean 2,4</td>
<td>182.7</td>
<td>178.2</td>
<td>182.9 185.1 183.9 184.0</td>
<td>1.98</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Attention (% correct)</td>
<td>Mean 2,4</td>
<td>96.8</td>
<td>94.1**</td>
<td>95.4 96.0 96.6 96.0</td>
<td>0.148</td>
<td>log(101 – x)</td>
<td></td>
</tr>
<tr>
<td>Attention (number of errors)</td>
<td>Mean 2,4</td>
<td>5.6</td>
<td>11.9**</td>
<td>8.7 6.0 6.0 6.9</td>
<td>0.176</td>
<td>log(1 + x)</td>
<td></td>
</tr>
<tr>
<td>Cancellation (number correct)</td>
<td>Mean 2,4</td>
<td>94.7</td>
<td>90.8</td>
<td>90.8 97.0 98.0 95.3</td>
<td>2.65</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cancellation (number of errors)</td>
<td>Mean 2,4</td>
<td>2</td>
<td>7.5</td>
<td>7.2 6.9 7.7 8.2</td>
<td>7.6</td>
<td>0.203 sqrt(1 + x)</td>
<td></td>
</tr>
<tr>
<td>Critical flicker fusion (Hz)</td>
<td>Mean 2,4</td>
<td>4</td>
<td>6.4</td>
<td>9.2 6.6 8.6 10.3*</td>
<td>8.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two flash fusion (ms)</td>
<td>Mean 2,4</td>
<td>38.0</td>
<td>37.3</td>
<td>37.9 37.6 38.3 37.9</td>
<td>1.078</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choice reaction time (ms)</td>
<td>Mean 2,4</td>
<td>313.5</td>
<td>320.5</td>
<td>320.5 316.5 314.5 317.5</td>
<td>0.131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tapping (number of taps)</td>
<td>Mean 2,4</td>
<td>389.4</td>
<td>389.6</td>
<td>381.8 390.7 386.7 386.4</td>
<td>4.53</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tapping (involuntary rest pauses)</td>
<td>Mean 2,4</td>
<td>4</td>
<td>400.0</td>
<td>393.1 385.3 390.9 394.0 390.1*</td>
<td>4.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significance levels: *P < 0.05; **P < 0.01; ***P < 0.001.
DSST: digit symbol substitution test.
% correct: number of correct responses/total number of stimuli presented.
Number of errors: number of errors of omission and commission.
Standard errors are pooled estimates taken from the analysis of variance based on all treatments.
Where data have been transformed, standard error is given on the transformed scale.

s.e. of these two means
**Electroencephalograms**

Recordings with eyes open  No changes in the EEG were observed with bendrofluazide. Oxazepam reduced delta activity (P < 0.05) in derivation P3-01 when both post-ingestion sessions were meaned. Theta and alpha 2 activity were reduced (P < 0.05) in C3-T3 2 h after ingestion, accompanied by an increase in beta 1, while theta power decreased (P < 0.01) and beta 1 increased (P < 0.05) 4 h after ingestion. When post-ingestion sessions were meaned, oxazepam decreased theta activity (P < 0.01), while beta 1 was increased (P < 0.01).

Recordings with eyes closed  There were no changes in the EEG with bendrofluazide. Oxazepam reduced alpha 1 activity in C3-T3 at both 2 and 4 h after ingestion and when both sessions were meaned (P < 0.001). Alpha 2 activity was decreased 2 h after ingestion and when post-ingestion sessions were meaned (P < 0.001). Similarly, oxazepam decreased total alpha activity 2 h (P < 0.01) and 4 h after ingestion (P < 0.001), and when post-ingestion sessions were meaned (P < 0.001). These findings are shown in Figure 1.

Body sway  The results are shown in Table 3. Amplitude of body sway with eyes open in the frequency range 0.05–1 Hz was increased by bendrofluazide (2.5 mg, P < 0.05) and by oxazepam (P < 0.01) when post-ingestion sessions were meaned.

With eyes closed, no changes occurred with any dose of bendrofluazide, while oxazepam increased 0.05–1 Hz (P < 0.01) and 3.25–4 Hz (P < 0.05) activity when meaned over post-ingestion sessions.

Heart rate and blood pressure  Heart rate and both systolic and diastolic blood pressure were unaffected by any of the drugs (Table 4).

Plasma concentrations  Plasma concentrations for bendrofluazide are shown in Table 5.

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**Table 2** Effect of bendrofluazide on subjective assessment of mood and well-being (means over post-ingestion times for 12 subjects)

<table>
<thead>
<tr>
<th>PC</th>
<th>Placebo</th>
<th>Oxazepam 15 mg</th>
<th>Bendrofluazide (mg)</th>
<th>Mean</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC1</td>
<td>−0.078</td>
<td>0.133</td>
<td>−0.209</td>
<td>0.036</td>
<td>−0.167</td>
</tr>
<tr>
<td>PC2</td>
<td>−0.071</td>
<td>0.034</td>
<td>−0.248</td>
<td>−0.170</td>
<td>0.260</td>
</tr>
<tr>
<td>PC3</td>
<td>−0.103</td>
<td>0.210</td>
<td>0.102</td>
<td>0.316</td>
<td>0.189</td>
</tr>
<tr>
<td>PC4</td>
<td>−0.032</td>
<td>0.026</td>
<td>−0.023</td>
<td>−0.113</td>
<td>−0.271</td>
</tr>
</tbody>
</table>

PC1–4 are principal components with loadings representing the following assessments:
PC1: wakefulness, energy, alertness, concentration, efficiency, sociability.
PC2: calmness, relaxation, carefree feelings.
PC3: happiness.
PC4: irritability, passivity.
Significance levels: *P < 0.05; **P < 0.01; ***P < 0.001.
Standard errors are pooled estimates taken from the analysis of variance based on all treatments.

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**Table 3** Effects of bendrofluazide on amplitude of body sway (arbitrary units) (means over post-ingestion times for 12 subjects)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Placebo</th>
<th>Oxazepam 15 mg</th>
<th>Bendrofluazide (mg)</th>
<th>Mean</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eyes open</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05–1.0</td>
<td>290.7</td>
<td>301.8**</td>
<td>300.7*</td>
<td>290.7</td>
<td>294.7</td>
</tr>
<tr>
<td>1.25–2.0</td>
<td>157.2</td>
<td>156.0</td>
<td>168.0</td>
<td>159.7</td>
<td>157.1</td>
</tr>
<tr>
<td>2.25–3.0</td>
<td>76.0</td>
<td>76.4</td>
<td>78.2</td>
<td>76.1</td>
<td>76.7</td>
</tr>
<tr>
<td>3.25–4.0</td>
<td>43.3</td>
<td>46.0</td>
<td>46.2</td>
<td>43.3</td>
<td>41.4</td>
</tr>
<tr>
<td><strong>Eyes closed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05–1.0</td>
<td>305.2</td>
<td>318.4**</td>
<td>306.3</td>
<td>301.3</td>
<td>308.8</td>
</tr>
<tr>
<td>1.25–2.0</td>
<td>183.8</td>
<td>190.6</td>
<td>184.8</td>
<td>184.4</td>
<td>184.9</td>
</tr>
<tr>
<td>2.25–3.0</td>
<td>92.7</td>
<td>102.0</td>
<td>98.9</td>
<td>96.7</td>
<td>96.9</td>
</tr>
<tr>
<td>3.25–4.0</td>
<td>51.3</td>
<td>58.5*</td>
<td>56.0</td>
<td>50.1</td>
<td>53.5</td>
</tr>
</tbody>
</table>

Significance levels: *P < 0.05; **P < 0.01.
Standard errors are pooled estimates taken from the analysis of variance based on all treatments.
Where data have been transformed, standard error is given on the transformed scale.
Square root transform applied to raw data.
Figure 1  Effects of bendrofluazide on the EEG at 2 and 4 h after drug ingestion. [Z] indicates change at 2 and 4 h from pre-ingestion value with placebo. [□] indicates the effect of each dose of the drugs compared with placebo in the following manner: at 2 and 4 h after ingestion, the difference from pre-ingestion means were calculated, and these changes subtracted from the change in placebo means from pre-ingestion to each post-ingestion time. Differences are based on mean values for 12 subjects. Significance levels: *P < 0.05; **P < 0.01; ***P < 0.001.

Table 4 Effects of bendrofluazide on blood pressure and heart rate (means for 12 subjects)

<table>
<thead>
<tr>
<th>Time after ingestion (h)</th>
<th>Placebo</th>
<th>Oxazepam</th>
<th>Bendrofluazide (mg)</th>
<th>Mean</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15 mg</td>
<td>2.5</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>2</td>
<td>71.8</td>
<td>70.9</td>
<td>74.4</td>
<td>70.0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>73.7</td>
<td>72.0</td>
<td>72.5</td>
<td>76.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75.0</td>
<td>74.6</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>2</td>
<td>132.7</td>
<td>129.0</td>
<td>130.8</td>
<td>131.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>132.3</td>
<td>128.5</td>
<td>127.8</td>
<td>130.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>128.7</td>
<td>129.0</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>2</td>
<td>63.8</td>
<td>64.3</td>
<td>62.0</td>
<td>64.7</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>62.0</td>
<td>61.7</td>
<td>60.0</td>
<td>62.4</td>
</tr>
</tbody>
</table>

Significance levels: *P < 0.05; **P < 0.01.
Standard errors are pooled estimates taken from the analysis of variance based on all treatments.
Where data have been transformed, standard error is given on the transformed scale.
*Log(x – 30) applied to raw data.

Table 5 Plasma concentration (ng ml⁻¹) of bendrofluazide (means for 12 subjects)

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Time after ingestion (h)</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td></td>
<td>22.2</td>
<td>15.5</td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td>31.8</td>
<td>24.5</td>
</tr>
<tr>
<td>10.0</td>
<td></td>
<td>69.5</td>
<td>49.3</td>
</tr>
</tbody>
</table>

Discussion

The present findings have demonstrated changes in some aspects of psychomotor performance and body sway with bendrofluazide. These were evident as an increase in the number of errors in letter cancellation and a reduced rate of finger tapping. The amplitude of body sway increased, although this effect occurred
only at the lowest dose. There were however no changes in the EEG, sustained attention, memory or subjective assessment of mood. In contrast, the active control drug oxazepam modified the EEG and impaired sustained attention and finger tapping, whilst also increasing body sway.

Despite the known incidence of adverse effects of thiazide diuretics in the patient population [10] including lethargy and fatigue [11, 12], few systematic studies addressing the issue of central effects of these drugs have been carried out. Often multiple therapies including a diuretic have been administered, with the primary purpose of the study to investigate effects of other drugs such as β-adrenoceptor antagonists and angiotensin converting enzyme inhibitors.

It has therefore been difficult to establish whether central effects occur with diuretics administered alone. Motor performance, reaction time and colour matching in baboons were unaffected by treatment with hydrochlorothiazide and triamterene [13]. Memory function in hypertensive patients receiving diuretic medication was similarly unchanged compared with normotensive data, in contrast with deficits related to methylpap and propranolol treatment [14]. No changes in cognitive ability assessed by the Wechsler Adult Intelligence Scale were seen with furosemide administered to normotensive individuals [15]. Concomitant therapy with hydrochlorothiazide [16] did not affect cognitive performance and memory in patients treated with enalapril.

Nevertheless some studies have suggested the possibility of effects, although not with single agents. Hydrochlorothiazide and amiloride increased Type A behaviour characteristics, generally associated with greater risk of cardiovascular disease, while atenolol had the reverse effect [17]. Croog et al. [18] reported that hydrochlorothiazide modified the effects of captopril, propranolol and methyldopa on quality of life, where apparent improvements in well-being with captopril were attenuated by the diuretic.

The majority of investigations have involved multiple therapies and chronic drug ingestion in hypertensive patients, where confounding factors exist including changes with time and effects of hypertension. In the light of this, there appears to be little evidence for centrally mediated side effects with diuretics per se.

The present study involving acute ingestion of bendroflumazide in healthy volunteers has used a schedule of tests known to be sensitive to the central effects of drugs [1–5]. In view of the absence of change in the EEG and tests of attention and memory, a central effect of bendroflumazide is considered to be unlikely. The changes in body sway and psychomotor performance seen with bendroflumazide may be related to peripheral effects.

In conclusion, we have been unable to establish central effects with the diuretic, bendroflumazide, and there was no evidence of sedation or reduced vigilance. The present investigation is part of a programme of studies with healthy volunteers to identify the potential central effects of antihypertensive medication, in which we have previously demonstrated that angiotensin converting enzyme inhibitors and calcium antagonists are free of sedation and impaired psychomotor performance. Given the availability of such therapy, any adverse change in psychomotor performance with bendroflumazide irrespective of whether it is centrally or peripherally mediated should be considered when choosing therapy for individuals with mild hypertension who are engaged in skilled activities.

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References

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