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# DIFFERENCES IN PSYCHIC PERFORMANCE WITH GUANFACINE AND CLONIDINE IN NORMOTENSIVE SUBJECTS

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**1** Doses of clonidine 0.15 mg or guanfacine 1.0 mg, respectively, and 2 h later additional doses of clonidine 0.3 mg or guanfacine 2.0 mg, respectively, were given to 24 healthy students.

**2** Blood pressure was reduced by the same amount by both drugs.

**3** Plasma noradrenaline concentrations decreased with both drugs, but the reduction was significantly greater following the administration of clonidine.

**4** Mental activity in the EEG was less suppressed in the guanfacine group than in the clonidine group. The differences were statistically significant.

**5** Self-estimations for well-being and mood showed only small changes due to guanfacine but significant changes due to clonidine.

**6** The decrease of information processing and the increase in reaction time, measured by performance in different psychometric tests, were significantly more pronounced after clonidine treatment than guanfacine.

**7** A dose-response relationship could only be observed in vigilosomnograms, in the tests of self-estimation related to well-being and mood and in the decrease in plasma noradrenaline in the clonidine group.

**8** It was concluded that guanfacine had a lesser CNS depressant action than clonidine, when administered in equipotent hypotensive doses.

## Introduction

GUANFACINE, a new antihypertensive agent, is a phenylacetylguanidine derivative (Bream, Lauener, Picard, Scholtysik & White, 1975). It possesses pharmacological properties similar to those of clonidine, a derivative of imidazoline, which is a central α-adrenoceptor agonist (Sattler & van Zwieten, 1967; Schmitt, Schmitt, Boissier & Guidicelli, 1967; Schmitt, Schmitt & Fenard, 1973; Loew & Waite 1974; Reid, Tangri, & Wing, 1977). Guanfacine differs from clonidine in that it does not lead to a reduction in the dopamine transformation in the corpus striatum of the rat (Scholtysik, Lauener, Eichenberger, Bürki, Salzmann, Müller-Schweinitzer & Waite, 1975). The local administration of guanfacine into the medulla oblongata of the cat has no effect on blood pressure and heart rate (Saameli, Scholtysik & Waite, 1975) and there is no indication of a sedative effect in the EEG of the rat (Kleinlogel, Scholtysik & Sayers, 1975). In experiments on dogs (Scholtysik *et al.*, 1975) as well as on humans (Kirch & Distler, 1978; Roeckel, Sabel & Heidland, 1978), guanfacine has little sedative action but is an effective hypotensive drug. Generally in the treatment of hypertension with centrally acting α-adrenoceptor agonists, tiredness has frequently been quoted as a troublesome side-effect (Putzeys, Hoobler & Arbor, 1972; Laverty, 1973; McMahon, Ryan, Jain, Vargas & Vanov, 1978; Page, Yager & Sidd, 1976; Brunner, Djawan, Dorda,

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Penner & Grabner, 1977; Jain, Ryan, Vargas & MacMahon, 1977; Walker, Shah, Ramanathan, Vanov & Helfant, 1977; Hall, Goedel-Meinen & Rudolf, 1978; Keränen, Nykänen & Taskinen, 1978).

Previous experiences of sedation with clonidine have been reported by Anlauf, Hoerson, Hampel & Merguet, (1973), Dollery, Davies, Draffan, Dargie, Dean, Reid, Clare & Murray, (1976), Davies, Wing, Reid, Neill, Tippett & Dollery, (1977) and Wing, Reid, Davies, Neill, Tippett & Dollery, (1977). Ashton & Rawlins (1978) have studied its effect on vigilance using the EEG.

Clonidine leads to a reduction in plasma noradrenaline (Louis, Doyle, Anavekar, Johnston, Geffen & Rush, 1974; Hökfelt, Hedeland & Dymling, 1970; Hökfelt, Hedeland & Hansson, 1975; Wing, Reid, Hamilton, Davies & Dollery, 1976; Metz Halter, Porter & Robertson, 1978; Whitsett, Chrysant, Dillard & Anton, 1978). A relationship between the reduction in noradrenaline concentration and psychometric side effects has been reported (Lidbrink, 1974; Henning, 1977; Reid *et al.*, 1977). An effect of guanfacine on plasma noradrenaline in man has been reported in only one study by Zamboulis, Hamilton & Reid (1978).

In the present study we have investigated the effects of guanfacine and clonidine on plasma noradrenaline concentration in relation to their psychometric side-effects.

## Methods

### *Subjects*

Twenty-four male students with an average age of 24 yr (mean $\pm$ s.d. $23.8 \pm 2.8$yr) were selected because they had a normal blood pressure and were psychologically stable. Their resting systolic blood pressure ranged from 120 to 130 mm Hg and subjects whose pressure fell below 120 mm Hg after 2 min of deep stooping followed by standing for 3 min were rejected. Their pulse rate varied only within $\pm 4$ beats/minute.

Subjects who complained of being affected by the weather, morning weariness and anorexia were rejected. Their psychic stability was measured with the Eysenck Personality Inventory (Eysenck, 1964) without considering extraversion or introversion by normal mendacity-score. After being instructed about the German laws for pharmaceutical products, all students consented to participate in the test.

### *Drugs*

Guanfacine and clonidine were tested in a randomized double-blind cross-over study. The drugs were given orally in capsules of identical appearance. Each capsule contained guanfacine 1 mg or clonidine 0.15 mg. On the first day of the test series 12 participants received guanfacine 1 mg and 2 h later a further dose of guanfacine 2 mg. The other group of 12 participants received clonidine 0.15 mg and 2 h later a further dose of clonidine 0.3 mg. The seond test series took place 2 weeks later with the order of doses reversed.

### *Test procedures*

Blood pressure was measured using a standard sphygmomanometer in the sitting position.

Plasma noradrenaline concentration was measured fluorometrically for 14 participants according to the method of Renzini, Brunori & Valori (1970) with modifications described by Brecht, Banthien & Schoeppe (1976). Forearm venous blood for the determination of plasma noradrenaline concentration was obtained under standardized conditions after each test session. Samples were taken after an EEG recording or after psychometric testing.

The EEG was recorded using a Sn-ei system which was specially balanced between the amplifiers. The electrodes (Schwarzer Ltd) were fastened with collodium to record from two lower bipolar parasagittal positions. The records were evaluated in the form of vigilosomnograms (Kugler, Johannes, Laub & Tulowein, 1978). All consecutive EEG epochs of 40 s were classified into the EEG stages of sleep (0–4) according to the classification of Rechtschaffen & Kales (1967). The percentage of each stage of sleep was read from an interval spectrogram.

A subjective self-estimation of the effect of the drug was made using Janke's Questionnaire (1964). The rating ranged from very active to very apathetic and the eagerness to work from very eager to work to very reluctant to work.

The semantic differential of Hofstätter (1967) was modified for the self-evaluation of well-being and mood. The main variables aggression, excitement, hate, menace, envy, sorrow, depression, sadness, sedation and tiredness were subjected to factor analysis to derive an effective emotional scale. The basic variables were prepared in the preliminary test period for evaluation on a scale from 1–7 for 24 polar qualities. Similarly during the study of the drugs, a rating of the aforementioned variables, well-being and mood, was carried out.

The 'Zahlen-Verbindungs-Test' according to Oswald (1978), records the time taken to assimilate information. In this test 24 numbers were arranged randomly in a circle and had to be connected in ascending order. The time needed for completion of the task was recorded.

The Pauli-adding-up-test according to Kraepelin-Pauli (Arnold, 1961) was used as a multi-dimensional test, mainly to determine the ability to concentrate. In addition to the commonly used test there was an

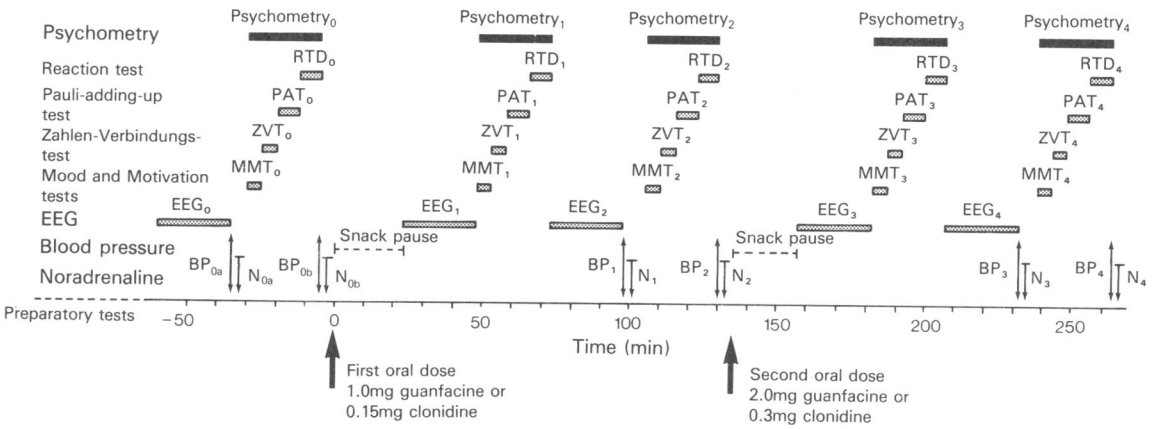


**Figure 1** Time schedule for all tests and parameters in the study. Mood and motivation tests (MMT) include direct subjective self-estimations and semantic differential.

electronic modification which permitted the measurement of the time required to complete each problem. For 8 min the participants had to add two lighted numbers randomly chosen and to insert the last digit of the sum into a decimal keyboard.

The reaction-time-test (Mierke, 1956) was carried out using a recording device (Seus, 1968; Seus & Seus, 1972), on-line to a Nova calculator. For 8 min, the subjects had to react as quickly as possible by pushing one of five differently coloured keys, while the corresponding colour signal appeared on a lighted screen. The colour signal could be seen for 0.8 s and was then followed by a break of 0.8 seconds. A key depression during the signal was rated as a correct hit, while a correct decision, made in the break following a signal, was counted as a late reaction. A late depression of the key, that is, the key was pressed after the appearance of the next signal colour, or an error was counted as an incorrect answer. The interval between the switching on of a signal and the appropriate key-pushing was defined as reaction time.

All participants achieved 90–100% correct responses in the allotted time. In the described form the test aims to evaluate processes of visual perception and integrative assimilation.

Shortening the time interval between the sequence of signals produced acute stress (Maiwald, Mayer & Ruscht, 1977), which was aggravated by allotting a prize for 'success in this situation'. Rivalry between two volunteers, the better one got the prize, amplified the stress.

The aim of this test was to study the stress-suppressing effect of the two drugs.

*Time schedule*

The Zahlen-Verbindungs-Test and the Pauli-adding-up-test were practised by each participant for 10 min before the scored test to exclude learning effects during the experiment. The EEG electrodes and the venous sampling needle were placed in position during the practise period. The test started at 1640 each day for two volunteers simultaneously to avoid vigilance variation according to the day's rhythm (Jovanovic, 1976).

The initial examinations took place in the following sequence (Figure 1): electroencephalogram ($EEG_0$), blood pressure ($BP_{0a}$ before, $BP_{0b}$ after psychometrics), plasma noradrenaline ($PNA_{0a}$ before, $PNA_{0b}$ after psychometric tests); psychic-condition-test ($PCT_0$), including actual mood and semantic differential; Zahlen-Verbindungs-Test ($ZVT_0$); Pauli-adding-up test ($PAT_0$); reaction-time-test ($RTD_0$).

After this test series the first capsule was given. The first control series of tests then began 22 min later. During the pause a light meal was given consisting of bread and butter with a slice of sausage, and some herb-tea.

The series of tests was then repeated 135 min after dosing, and then two more capsules of the same agent were given. The exact test timings are in Figure 1.

At the end of a session the subjects were observed for an additional 2–3 h and asked for their opinion about the drug.

*Statistics*

Not all of the tests results could be analyzed using parametric statistics. Vigilosomnograms, correct answers, incorrect answers and late reactions were examined between the groups in $2 \times 4$ and $2 \times 3$ contingency tables, respectively, according to their different frequency distribution. The differences of frequencies between and within the groups were tested using Wilcoxon matched pairs, the signed rank test and the Spearman rank correlation test. The

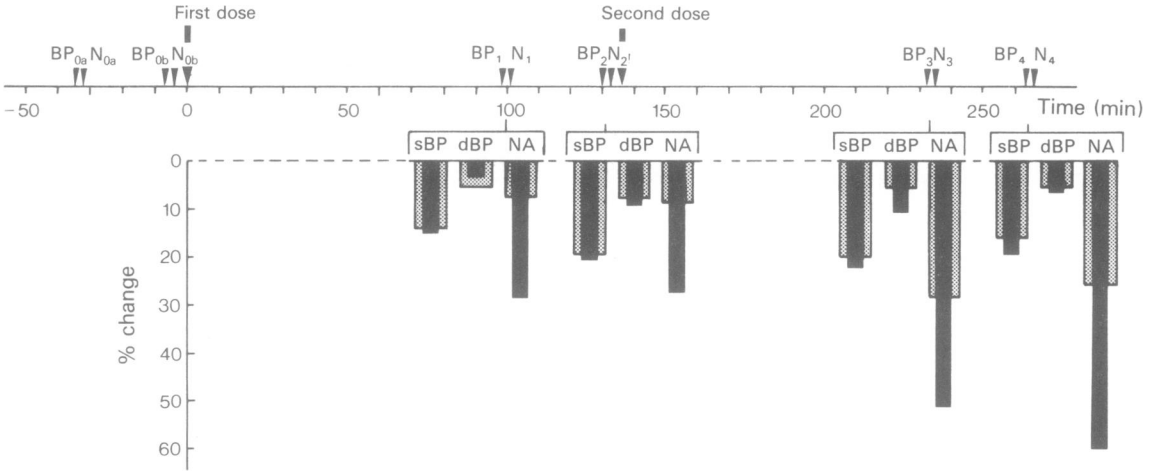


**Figure 2** Percentage changes in systolic blood pressure (sBP), diastolic blood pressure (dBP) and noradrenaline (NA) from initial values after clonidine (solid) or guanfacine (stippled). Statistically significant differences are shown in Tables 2 and 3.

dynamics of mood were tested using a Q-factor analysis with Varimax rotation (Harman, 1960).

## Results

### *Blood pressure and plasma noradrenaline*

The administration of psychometric tests, before drugs were given to both groups of subjects, did not produce any significant effects on either blood pressure or plasma noradrenaline concentration (Table 1). The hypothesis that a stress situation could be created by means of high signal rates during the psychometric testing period on the determination device and that this would result in a blood pressure increase could not be verified. With the chosen doses of guanfacine and clonidine, an almost identical decrease in blood pressure occurred during the whole test period (Table 2; Figure 2).

Guanfacine and clonidine had significantly

**Table 1** Means and s.d. of both groups for blood pressure and plasma noradrenaline after resting EEG, before psychometric testing ($O_a$) and after psychometric testing ($O_b$).

| | | *Period* $O_a$ | $O_b$ | *Significance* |
|---|---|---|---|---|
| Blood pressure (mmHg) ($n = 2 \times 24$) | Mean | 124.3/81.8 | 125.7/82.0 | NS |
| | s.d. | 3.0/2.0 | 2.7/1.6 | |
| Plasma noradrenaline ng/l) ($n = 2 \times 14$) | Mean | 345.0 | 383.3 | NS |
| | s.d. | 72.9 | 90.4 | |

**Table 2** Means and s.d. of blood pressure (mmHg) for both drug groups according to time schedule (Figure 1)

| *Drug* | | *Period* $O_a$ | *1* | *2* | *3* | *4* |
|---|---|---|---|---|---|---|
| Guanfacine | Mean | 124.3/82.1 | 106.8/77.8 | 100.1/75.7 | 99.3/77.5 | 104.2/77.8 |
| | s.d. | 3.0/2.0 | 5.6/3.7 | 4.4/4.6 | 3.3/3.1 | 6.9/7.9 |
| Clonidine | Mean | 124.3/81.9 | 106.0/78.9 | 98.8/74.0 | 96.8/73.0 | 99.9/76.5 |
| | s.d. | 2.9/1.9 | 4.3/4.0 | 3.3/5.8 | 4.3/6.5 | 4.7/7.4 |
| Significance | | NS | NS | NS | NS | NS |

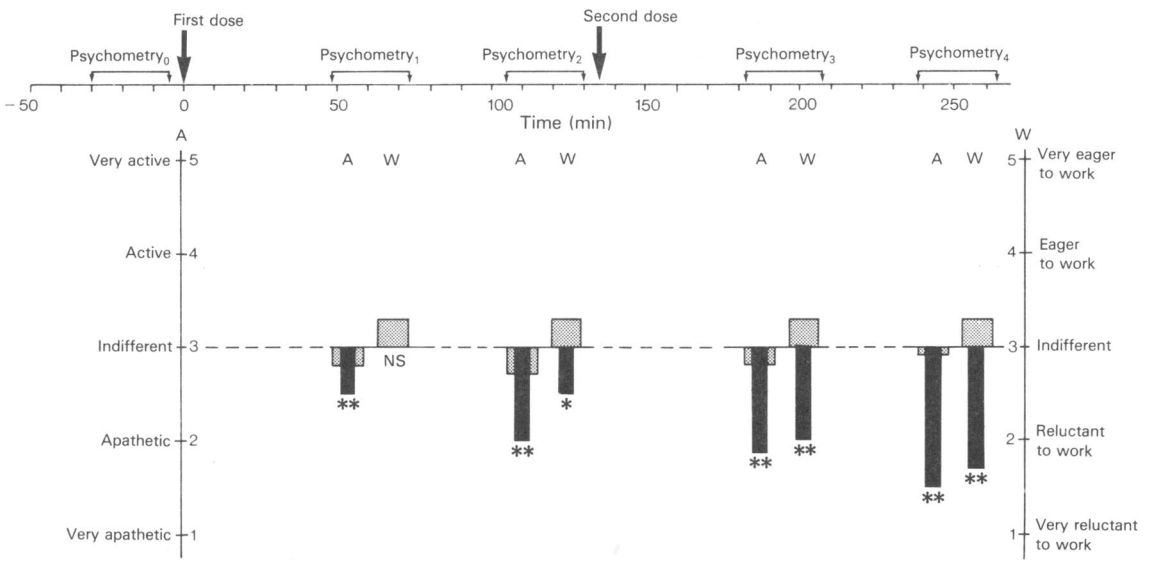


**Figure 3** Subjective estimation for activity (A) and eagerness to work (W) after clonidine (solid) or guanfacine (stippled. Statistically significant differences exist between two drugs: $*P \leqslant 0.05$; $**P \leqslant 0.001$; NS, not significant.

different effects on plasma noradrenaline concentrations. Both drugs produced a decrease in plasma noradrenaline concentration, but the reduction after clonidine was significantly greater. Whereas a significant decrease of plasma noradrenaline concentration only occurred after the second oral dose of guanfacine, a significant decrease in plasma noradrenaline concentration occurred after the first dose of clonidine (Table 3; Figure 2).

*Vigilance*

From the percentage incidence of EEG stages of sleep, the guanfacine-treated group seemed more alert during the test period than the clonidine treated group (Table 4). The second dose of clonidine caused a significant reduction in alertness.

*Mood and Motivation*

The results of subjective self-estimation showed that eagerness to work was at first slightly increased in the guanfacine group, but during the course of the experiment this was estimated as constant. Clonidine caused a clear reduction in the eagerness to work, so that at the end of the experiment there was a difference of 1.6 scores on the rating scale between the guanfacine and the clonidine group. The same trend was reflected in the subjective self-estimation of the drug's effect on the very active to very apathetic scale (Figure 3).

The interpretation of Hofstätter's semantic differential identified two main factors, 'affliction' represented by the horizontal axis and 'activity' by the vertical axis in Figure 4. The other basic factors were then plotted in their relevant positions according to whether they were active or passive and relieved or afflicted (Figure 4).

Throughout the test the variables for 'well-being' and 'mood' were similar in both groups. The guanfacine group showed a relatively different starting position in the factorial model and was free of affliction. This position did not alter after the first or second dose.

**Table 3** Means and s.d. of plasma noradrenaline (ng/l; $n = 14$) for both drug groups according to time schedule

| | *Period* | | | | |
|---|---|---|---|---|---|
| | $O_a$ | *1* | *2* | *3* | *4* |
| Guanfacine | 340 ± 77.8 | 315 ± 95.3 | 310 ± 80.2 | 243 ± 74.1 | 252 ± 67.5 |
| | | | $P < 0.05$ | | |
| Clonidine | 347 ± 82.4 | 249 ± 62.8 | 252 ± 42.7 | 168 ± 44.2 | 140 ± 35.5 |
| | | $P < 0.005$ | | | |
| Significance | NS | < 0.05 | < 0.05 | < 0.001 | < 0.001 |

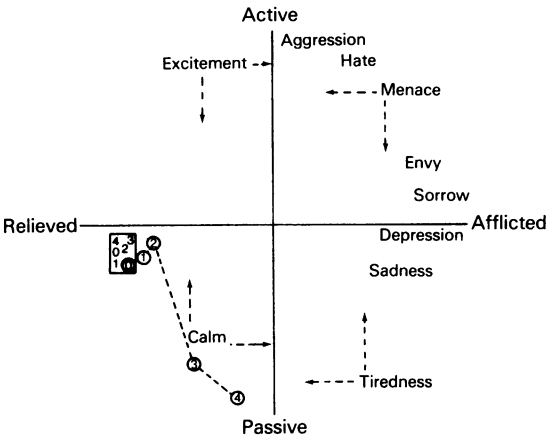


**Figure 4** The 'semantic differential' by Hofstätter (1967) is used in the form of a factor analysis describing psychic conditions and feelings. The dynamics of mood are projected in the factor by the numbers 0–4 inthe guanfacine group and ⓪–④ in the clonidine group (⓪ = before application; ①–④ = after application). Further explanations are discussed in the text.

The clonidine group resembled that of the guanfacine until the second dose. After the second dose, well-being and mood were projected towards the pole of inactivity and therefore to an emotionally ineffective attitude. This could be interpreted as an increase in apathy.

*Information-processing and reaction-time*

After the first dose of guanfacine the 'Zahlen-Verbindungs-Test' showed an initial improvement of 4.7 s in working time, and this continued after the dose. In the clonidine group, despite a similar initial reduction of about 2.9 s, the working time 115 min after the first dose was about 7.3 s longer than before (Table 5; Figure 5). The difference was significant from 115 min onwards.

**Table 4** Percentage incidence of EEG stages (0 = wakefulness, 4 = deep sleep) for both drug groups according to the time schedule (Figure 1)

| *EEG stages* | | *Period* | | | | |
|---|---|---|---|---|---|---|
| | | *0* | *1* | *2* | *3* | *4* |
| 0 | Guanfacine | 68.3 | 74.7 | 66.9 | 79.8 | 69.0 |
| 1 | | 27.1 | 22.2 | 28.9 | 19.7 | 22.4 |
| 2 | | 4.6 | 3.0 | 4.5 | 0.4 | 5.1 |
| 3 | | 0 | 0.1 | 0.1 | 0 | 3.2 |
| 4 | | 0 | 0 | 0 | 0 | 0 |
| 0 | Clonidine | 67.5 | 55.8 | 54.9 | 59.5 | 34.2 |
| 1 | | 26.4 | 35.8 | 35.1 | 25.3 | 36.0 |
| 2 | | 5.2 | 5.5 | 9.7 | 13.7 | 23.7 |
| 3 | | 0.8 | 2.5 | 0.2 | 1.3 | 5.8 |
| 4 | | 0 | 0.4 | 0 | 0 | 0 |
| Significance (for all stages) | | NS | 0.01 | NS | 0.005 | 0.001 |

In the Pauli-adding-up-test, the average addition time for ten single calculations after guanfacine showed a non-significant increase of 1.9 s until the third measurement, and then decreased to its initial value by the end of the experiment. In the clonidine group, the increase of addition time at the first measurement, 2.1 s, was significant; and this increased to 3.7 s by the third test (Table 5; Figure 5). After the second measurement the differences between the drug groups were significant ($P \leq 0.05$).

The mean reaction time for ten signals in the

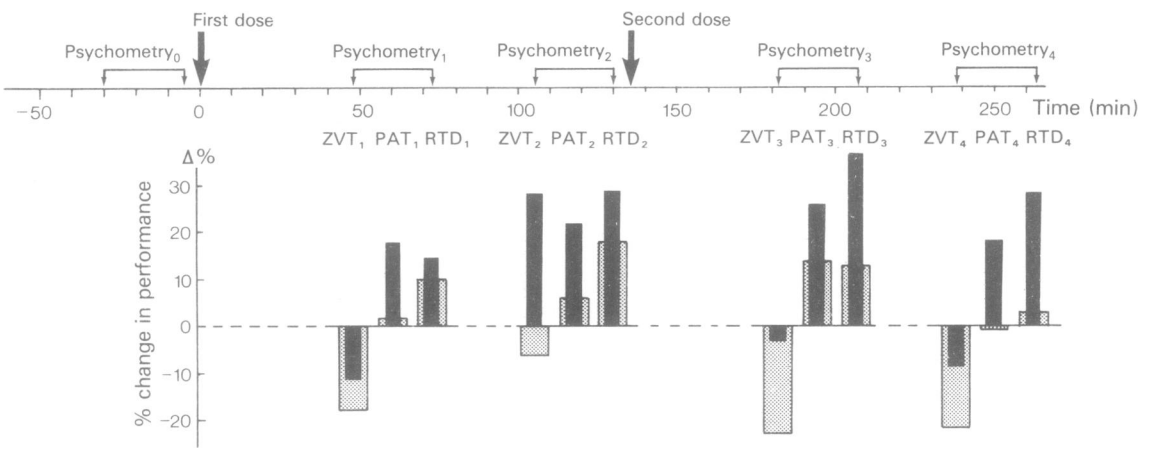


**Figure 5** Percentage changes to initial values after clonidine (solid) or guanfacine (stippled) for the time needed in the 'Zahlen-Verbindungs-Test' (ZVT), Pauli-adding-up-test (PAT) and reaction-time-test (RTD). Statistically significant differences are shown in Table 5.

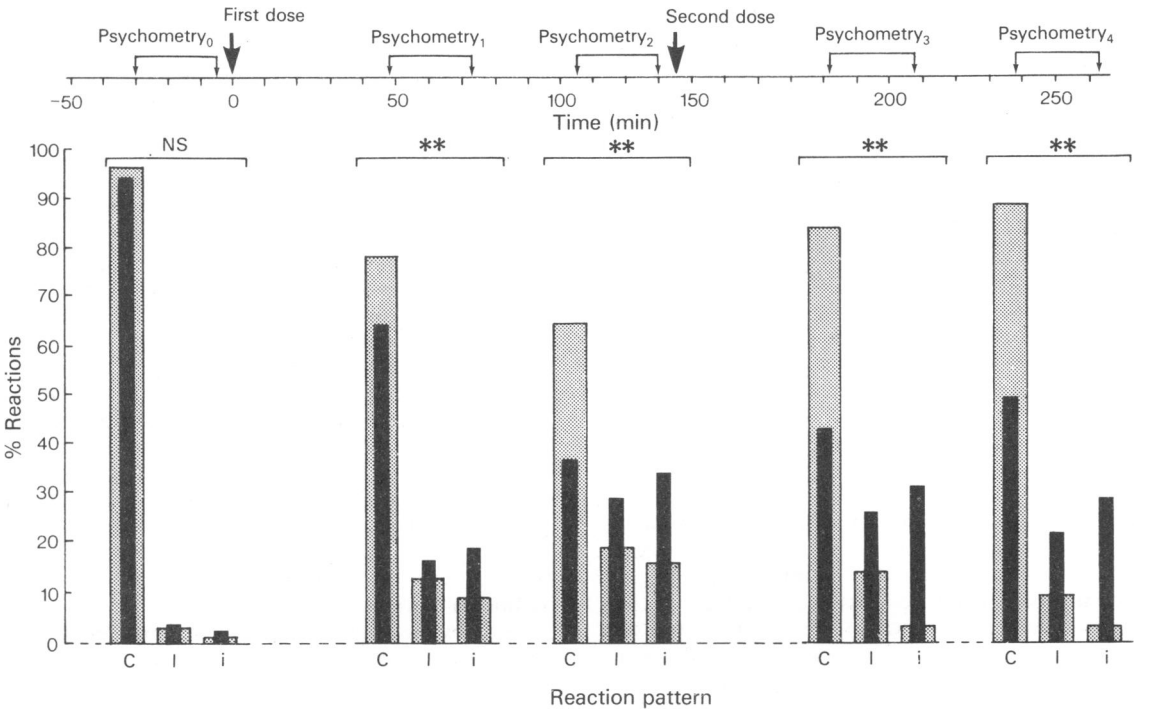


**Figure 6** Percentages of correct (c), late (l) and incorrect (i) reactions during the reaction test before and after clonidine (solid) or guanfacine (stippled). At each time after drug, the differences between the groups were highly significant: Apperception(capability of concentration). $^{**}P \leqslant 0.001$; NS, not significant.

**Table 5** Means and s.d. of psychometric testing according to the time schedule (Figure 1). PAT, Pauli-adding-up-Test; RTD, Reaction-time-test; ZVT, Zahlen-Verbindings-Test.

| | | *Period* | | | | |
|---|---|---|---|---|---|---|
| | | *0* | *1* | *2* | *3* | *4* |
| Response times (ZVT) (s) | Guanfacine | 26.6 ± 7.5 | 21.9 ± 8.8 | 24.2 ± 9.4 | 20.6 ± 5.8 | 20.9 ± 3.3 |
| | Clonidine | 25.7 ± 6.4 | 22.8 ± 5.1 | 33.0 ± 18.4 | 24.9 ± 9.4 | 23.6 ± 5.1 |
| | Significance | NS | NS | 0.001 | 0.001 | 0.05 |
| Response time/10 additions (PAT) (s) | Guanfacine | 13.7 ± 2.6 | 13.9 ± 2.9 | 14.5 ± 2.3 | 15.6 ± 2.5 | 13.6 ± 2.7 |
| | | | NS | | | |
| | Clonidine | 14.1 ± 2.7 | 16.2 ± 2.9 | 17.2 ± 3.4 | 17.8 ± 3.6 | 16.7 ± 4.6 |
| | | | $P < 0.05$ | | | |
| | Significance | NS | NS | 0.05 | 0.05 | 0.01 |
| Reaction time/10 signals (RTD) (s) | Guanfacine | 5.2 ± 0.6 | 5.7 ± 0.8 | 6.2 ± 0.8 | 5.9 ± 0.8 | 5.4 ± 0.6 |
| | | | $P < 0.005$ | | | |
| | Clonidine | 5.2 ± 0.7 | 6.0 ± 0.8 | 6.8 ± 0.9 | 7.2 ± 0.5 | 6.7 ± 0.6 |
| | | | $P < 0.001$ | | | |
| | significance | NS | < 0.05 | < 0.01 | < 0.001 | < 0.001 |

guanfacine group increased by 1 s during the first 2 h after the first dose. After the second dose, it decreased to approximately the initial value (Figure 5). In the clonidine group an increase of 0.8 s occurred, which increased a maximum of 2.0 s; and at the end of the experiment it was about 1.5 s (Table 5).

In the guanfacine group, the number of correct, late and incorrect reactions in the reaction test changed only slightly during the first period. The number of late responses was always greater than the incorrect ones (Figure 6). After clonidine the situation was reversed. The analysis of correct, late and incorrect reactions showed highly significant differences in favour of guanfacine ($P \leq 0.001$) over clonidine at all times during the test period (Figure 6).

## Discussion

Blood pressure measurements after both medications indicated that an equipotent hypotensive dose of each drug was administered. Plasma noradrenaline concentrations decreased less after guanfacine than after clonidine. There was no proof of a consistent correlation between plasma noradreanline concentration and psychoexperimental variables. No additional information was gained by testing these variables using a factor analysis.

The results of the mood and motivation tests and of the psychometric experiments showed that clonidine had a much greater sedative effect than guanfacine. This difference was also seen in the vigilosomnograms. The participants perceived the difference between the two drugs to such an extent that they could clearly distinguish both drugs restrospectively after completion of the test series. Similar observations on sedation with respect to clonidine have been reported by Anlauf *et al.* (1973). Differences between both drugs have also been mentioned by Kirch & Distler (1978). The different degree of sedation observed with the two drugs correlating with the decrease in plasma noradrenaline concentration.

The onset of hypotensive effect of clonidine, following an oral dose, occurs much more rapidly than with clonidine. The difference in rapidity of onset is probably related to the speed of entry of the drug into the brain. Interpretation of psychometric tests at different time intervals after the dose must take into account the differences in rate of onset of action.

Within the factor model only the additional double dose of clonidine could be distinguished in the projected feelings of well being and mood. The variables shifted from the initial value towards inactivity and apathy.

The ratio between dosage and efficiency can also be observed in the different incidence of EEG stages and vigilosomnograms. A remarkable dose-dependent decrease in plasma noradrenaline concentration was observed in the clonidine group. The other results of psycho-experimental testing showed no pronounced dose-dependent change despite increased dosage.

There were differences in perceptive, cognitive and reactive mental functions after clonidine and guanfacine administration, but there was no dose dependence. In contrast to this, a dose dependency was shown by dynamics of mood and the vigilosomnograms.

The obvious differences between both drugs raise the question whether the decrease in the plasma noradrenaline level by more than 30–50% below the initial value after the second dose of clonidine represents a threshold below which other processes occur or an additional central nervous action is initiated. Post-experimental observations by the investigating psychiatrist showed that only after clonidine did the participants lose their ability to concentrate. They could no longer articulate clearly, appeared to be apathetic and lost their self-control.

In experiments with animals, Scholtysik *et al.* (1975) have shown that both drugs reduce sympathetic nervous activity, whereas only clonidine reduces the central nervous dopamine turnover. Kleinlogel *et al.* (1975) have discussed the possibility of different α-adrenoceptors. With respect to the identical course of blood pressure measurements, one can argue whether peripheral mechanisms do not play a larger role after doses of guanfacine, as has already been reported for clonidine by Henning (1977), Zaimis (1977), Starke (1977) and Borowski, Taube & Endo (1977).

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