CENTRAL NERVOUS SYSTEM DEPRESSANT ACTIONS OF CLONIDINE AND UK-14,304: PARTIAL DISSOCIATION OF EEG AND BEHAVIOURAL EFFECTS

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1 The effects in five normal subjects of a single dose of clonidine (300 µg), UK-14,304 (750 µg) and placebo on a subjective rating scale for alertness/sleepiness, the contingent negative variation (CNV), reaction time, blood pressure and heart rate were compared over 6 h in a double-blind study.

2 After both drugs there was a fall in systolic and diastolic blood pressure and in heart rate. These changes were maximal between 2 and 4 h and were greater after clonidine than after UK-14,304.

3 There was a progressive increase in subjective ratings of sleepiness after both drugs, commencing at 1 h and maximal between 2 and 4 h. This effect was more pronounced after clonidine than after UK-14,304. There was a close correlation between the fall in blood pressure and the change in subjective rating for sleepiness after both drugs. Behavioural sleep also occurred after both drugs.

4 Compared with placebo there was a decrease in CNV magnitude at 2 and 4 h after both drugs, associated with a lengthening of reaction time and consistent with the subjective and behavioural changes. Depression of CNV magnitude was more pronounced after clonidine than after UK-14,304.

5 In some subjects after both drugs there was an initial increase in CNV magnitude at 1.5 h, occurring at the same time as behavioural sleep and subjective ratings of sleepiness. Such a dissociation between CNV magnitude and subjective and behavioural effects of drugs in man has not previously been reported.

6 It was concluded that UK-14,304 causes less central nervous system depression than clonidine at this dosage, but also has a less marked hypotensive effect.

Introduction

Clonidine is a potent hypotensive drug. Its effects on the blood pressure are thought to be due largely to actions on the central nervous system, probably involving α -adrenergic receptors in the vasomotor centre (Lavery, 1973). However, clonidine also appears to have other central effects including a considerable sedative action (Dollery, Davies, Draffan, Dargie, Dean & Reid, 1976) and for some patients blood pressure control is achieved at the cost of unacceptable drowsiness. A drug with the same hypotensive potential as clonidine but without its sedative action would clearly have many advantages, and UK-14,304 (Pfizer) was considered as a possible drug in this category. UK-14,304 is an imidazole derivative chemically similar to clonidine (Figure 1). Like clonidine, it produces a transient rise followed by a prolonged fall in blood pressure after intravenous injection in animals; the fall in blood pressure is associated, in cats, with a decrease in spontaneous and

Figure 1 Structure of (a) clonidine and (b) UK-14,304.

evoked activity in the cervical sympathetic nerve, suggesting that the hypotensive actions are centrally mediated (R. Massingham, personal communication). The purpose of the present investigation was to compare the sedative and hypotensive effects of clonidine and UK-14,304 in normal subjects.

Methods

Subjects and drugs

Five normal male volunteer subjects aged 20–25 years took part in the study. Each attended on three occasions one week apart and took by mouth clonidine (300 µg), UK-14,304 (750 µg) or placebo in random order. The investigation was carried out double blind using identical capsules. All tests started at 09.00 h; all subjects had eaten their normal breakfast and were not taking any other medication.

Measurements

1. Subjective rating scale: subjects were asked to rate themselves on a 100 mm linear scale on which 0 mm represented 'wide awake', 50 mm represented 'normal wakefulness' and 100 mm represented 'almost asleep'.

2. CNV was measured as described by Ashton, Millman, Telford & Thompson (1974) with slight modifications. Briefly, subjects were presented with series of paired signals. The warning signal was a brief tone (frequency, 4000 Hz; duration 20 ms) and the imperative signal was a lower tone of longer duration (frequency, 1500 Hz; duration 400 ms) delivered through a loudspeaker. The subject was required to press a button in response to the imperative signal; this stopped the tone and gave a measure of reaction time. The paired warning and imperative signals were separated by an interval of 1.25 s and were presented at random intervals (6–10 s) in a series of ten, each series lasting 1 min 10 seconds. The subjects were instructed to keep their eyes fixed on a mark throughout each series. The EEG was derived between the left mastoid and vertex positions from two silver/silver chloride stick-on electrodes and was amplified by a Devices M19 recorder on DC setting with a purpose-built operational amplifier with a time constant of 9 s and a zero offset of 60 µV; an earth electrode was placed on the right mastoid. Eye movements were monitored from a nasion-mastoid configuration and any contamination of the vertex-mastoid record was compensated by a special circuit which added or subtracted a portion of the nasion-mastoid channel, thus cancelling out eye movement artefacts. The EEG output was fed into a PDP8 on-line computer and the average response to each series of ten paired signals was traced out by an X–Y recorder. The magnitude of the CNV thus obtained for each series was measured in terms of area and expressed in µVs.

3. Reaction time was recorded on a digital counter which was activated by the onset of the imperative tone and stopped by pressure of the subject on a button-switch held in his preferred hand. The mean reaction time for each series of ten signals was recorded in ms.

4. Blood pressure was measured automatically by a Roche Arteriosonde recorder.

5. Heart rate was monitored by an ECG recorded from chest electrodes.

Procedure

The subjects sat in a separate room; the recording apparatus was housed in an adjacent room, in communication with the subject room through a one-way window and via closed circuit television. Oral communication was maintained through an intercom system.

A brief standard explanation of the procedure was given and the scalp and ECG electrodes and the blood pressure cuff were applied. The subject then had a practice run, responding to a series of ten paired signals. After a resting period of 30 min, baseline measurements were taken. These consisted of two recordings, 10 min apart, of CNV, reaction time, blood pressure, heart rate and finger temperature. At the end of these, the subject filled in his self-rating scale. The drug was then administered and readings were repeated at 0.5 h, 1 h, 1.5 h, 2 h, 4 h and 6 h, two readings 10 min apart being taken each time, and the rating scale being filled in after the second of each pair of readings. The subjects remained sitting in the subject room until the end of the 2 h measurements, after which they left for lunch (with their recording electrodes still in position), returning to the laboratory for the 4 and 6 h measurements. After the last set of readings they were questioned concerning any subjective symptoms or side effects.

Results

Blood pressure

Mean blood pressure readings after the drugs and placebo are shown in Figure 2. After both drugs there was a significant fall in systolic and diastolic blood pressure maximal at 2 and 4 hours. The decrease in blood pressure was greater with clonidine, after which the mean maximal fall in systolic pressure was 26.9 mmHg (from 110.2 ± 5.95 to 83.3 ± 3.93 mmHg) and the maximal fall in diastolic pressure was 17.4 mmHg (from 72.2 ± 3.29 to 54.8 ± 4.37 mmHg). After UK-14,304, the maximal fall in systolic pressure was 18.9 mmHg (from 116.1 ± 5.47 to 97.2 ± 4.97 mmHg) and the maximal fall in diastolic pressure was 14.6 mmHg (from 77.4 ± 3.77 to 62.8 ± 3.76 mmHg).

Heart rate

Mean heart rate after the drugs and placebo are shown in Figure 3. Heart rate fell significantly after both drugs with maximal effects at 1.5–4 h. The fall in heart rate was greater with clonidine after which it fell

Figure 2 Systolic and diastolic blood pressure ($\pm$ s.e. mean) in five subjects after placebo (●), UK-14,304 (▲) and clonidine (○).

* Denotes significant differences from pre-drug level (* $P < 0.05$; ** $P < 0.01$; t -tests).

Figure 3 Heart rate ($\pm$ s.e. mean) in five subjects after placebo (●), UK-14,304 (▲) and clonidine (○).

* Denotes significant difference from pre-drug level (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; t -tests).

11.8 beats/min (65.4 ± 3.18 to 53.6 ± 5.24 beats/min at 2 h) than with UK-14,304 after which it fell 9.3 beats/min (from 64.5 ± 4.2 and 55.2 ± 2.53 beats/min).

Subjective rating scale

After both drugs most subjects were observed to be asleep at the time of the 1.5, 2 and 4 h measurements

and had to be awakened to perform the CNV and reaction time tasks and to fill in their rating scales.

The results of the subjective rating scales are shown in Figure 4. While the degree of alertness altered very little during the 6 h after placebo, all subjects showed a progressive and significant increase in ratings of sleepiness after both drugs. This sedative effect was apparent at 1 h, maximal at 2 and 4 h, and still evident, although with some signs of recovery, at

Figure 4 Subjective rating scores ($\pm$ s.e. mean) in five subjects after clonidine (O), UK-14,304 (▲) and placebo (●).

* Denotes significant differences from pre-drug rating (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; t -tests).

Figure 5 The mean $\pm$ s.e. mean effect of clonidine (O) and UK-14,304 (▲), on CNV magnitude in five subjects, shown as change from placebo level.

* Denotes significant difference from placebo ($P < 0.05$, t -tests).

6 hours. The effect of clonidine was greater than that of UK-14,304.

Over the 6 h there was a close correlation for the groups as a whole between the fall in systolic blood pressure and the change in subjective rating for sleepiness, after both clonidine ($r = 0.704$, $P < 0.001$, $a = 8.2$ mmHg, $b = 0.655$ mmHg mm $^{-1}$) and UK-14,304 ($r = 0.608$, $P < 0.001$, $a = 8.3$ mmHg, $b = 0.504$ mmHg mm $^{-1}$).

CNV magnitude

Changes in CNV magnitude after clonidine and UK-14,304 are shown in Figure 5. Compared with placebo

there was a significant ($P < 0.05$) decrease in CNV magnitude at 2 h and 4 h after clonidine. After UK-14,304 there was also a decrease in CNV magnitude at 2 and 4 h, but this fall was less marked than after clonidine and failed to reach significance at the 5% level. CNV magnitude returned to pre-drug levels at 6 h after both drugs. After placebo there was little change in CNV magnitude, which remained at 9.88 ± 0.29 μ V s, over the 6 h period except for a rise to 13.53 ± 2.46 μ V s at the 4 h reading when the subjects returned from lunch. This post-prandial rise was not seen after the subjects had taken either of the drugs. The changes in CNV magnitude suggest that both clonidine and UK-14,304 had a central

Figure 6 CNV tracings and subjective rating scales from one subject after UK14,304.

Note dissociation between subjective rating and CNV magnitude. Subject was behaviourally asleep before 1.5 h measurements but showed a large increase in CNV magnitude from pre-drug level. At 4 h subject was still asleep and showed a pronounced fall in CNV magnitude, but subjective rating was similar to 1.5 h.

depressant effect, maximal between 2 and 4 h, and that these effects were more pronounced after clonidine.

The decreases in CNV magnitude after the drugs were consistent with the sleeping behaviour and subjective rating scales at 2 and 4 h. However, at 1.5 h CNV magnitude was not always correlated with the degree of sleepiness. Three of the five subjects after UK-14,304 and two of the subjects after clonidine had a definite rise in CNV magnitude at 1.5 h, at a time when they rated themselves as sleepy and were objectively asleep between readings. Figure 6 shows CNV tracings and subjective ratings of one of these subjects, in whom CNV magnitude more than doubled, from a pre-drug level of 10.4 μ V s to 22.0 μ V s 1.5 h after UK-14,304 although the subject

fell asleep. Thereafter it fell to the very low level of 0.9 μ V s at 4 h, recovering to the pre-drug level at 6 hours. In these subjects, the drugs appeared to have a biphasic effect on CNV magnitude, with an early, short-lived stimulant effect followed by a longer lasting depressant effect. No such biphasic effect was apparent on the subjective measure or on behaviour. This dissociation between CNV magnitude and subjective and behavioural effects does not appear to have been reported before.

Reaction time

There was a large variation in reaction time between subjects. However, mean reaction time after placebo changed very little during the experiment (mean reaction time over the 6 h was 177.35 ± 4.14 ms). By contrast, reaction time was lengthened after both drugs, reaching a maximum at 2 h and returning to pre-drug levels at 6 h. After clonidine, the maximum mean increase in reaction time was 14.5 ms and after UK-14,304 it was 15.0 ms. Neither of these changes reached significance but they were in the expected direction and changed over the same time course as CNV magnitude.

Subjective symptoms

When questioned after the experiment, all subjects complained of a dry mouth after clonidine and three also noticed this after UK-14,304. A fall in salivary secretion after clonidine has previously been noted by Dollery *et al.* (1976). Other symptoms mentioned were drowsiness, faintness and weakness.

Discussion

The results of this double blind placebo trial show that single oral doses of both clonidine (300 μ g) and UK-14,304 (750 μ g) have cerebral depressant effects as evidenced by behavioural sleep, subjective rating scales, fall in CNV magnitude and lengthening of reaction time. Both drugs also caused a significant decrease in systolic and diastolic blood pressure and a fall in heart rate. UK-14,304 caused less central nervous system depression than clonidine but also a less potent hypotensive effect and the regressions of hypotensive response on subjective sleepiness were similar. Both drugs exerted their maximum effects on all variables between 2 and 4 h; clonidine appeared longer acting than UK-14,304 with less evidence of recovery at 6 hours. The time course of action of clonidine was comparable with the results of a pharmacokinetic study by Dollery *et al.* (1976).

The temporary dissociation between CNV magnitude and behavioural and subjective effects seen at 1.5 h after drug administration was an unexpected finding. CNV magnitude has been described as

providing a measure of alertness, involving both arousal and attention (McAdam, 1969; Rebert, 1972). It would be expected that when subjects are drowsy, and even asleep between measurements, CNV magnitude would be reduced, and many central depressant drugs including alcohol, barbiturates and benzodiazepines have been reported to cause a decrease in CNV magnitude while central stimulant drugs cause an increase in CNV magnitude (Ashton *et al.*, 1974; Ashton, Millman, Thompson & Telford, 1975, 1976; Tinklenberg, 1972; Hablitz & Borda, 1973; Tecce & Cole, 1974; Kopell, Tinklenberg & Hollister, 1972; Kopell, Wittner, Lande, Wolcott & Tinklenberg, 1974; Tecce, Cole & Savignano-Bowman, 1975). However, in the present study some subjects showed an increase in CNV magnitude at 1.5 h at a time when they rated themselves as sleepy and were in fact behaviourally asleep before and after

the measurements. It is possible that the dual effect of clonidine and UK-14,304 on the CNV may be analogous to the biphasic effect of these drugs on the blood pressure after intravenous injection.

The close correlation between the degree of sedation and the fall in blood pressure which were observed with both drugs might suggest that these two effects are mediated by similar mechanisms. However, the temporary dissociation between CNV magnitude and degree of sedation and the observation that some drugs such as diazepam lower the CNV with little fall in blood pressure (Ashton *et al.*, 1976) indicate that it may be possible to separate the therapeutic and sedative actions of clonidine and related compounds.

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