A SINGLE DOSE STUDY OF TRAZODONE WITH AN ASSESSMENT OF ITS EFFECT ON MOOD AND AROUSAL

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- 1 A pharmacokinetic study of a single oral dose of a new antidepressant (trazodone) is described, linked to an attempt to measure changes in mood and arousal induced by the drug in normal subjects.
- 2 The drug had a measurable effect on arousal, but not on mood. It caused bradycardia (compared with placebo) and this persisted through the following night's sleep. This effect has not been completely explained.
- 3 The technique of mood and arousal measurement employed in this study seems potentially useful.

Introduction

Trazodone (Roussel) is a new drug, chemically unrelated to any existing drug, which has been shown to have antidepressant, sedative and analgesic properties. It has been used as a sedative in the treatment of neurosis and was effective in controlling anxiety, was well tolerated and had few side effects (Udabe, 1973). It has also been used in larger doses to treat depression and was as effective as amitriptyline or imipramine though some of its effects were different and it acted rather more rapidly (Udabe, 1973). The combination of analgesic and sedative properties suggest that it could be of value for pre-medication or post-operatively and might be useful for endoscopy.

The purpose of this investigation was to establish blood levels attained after a single oral dose and to try to assess the effects of the drug on mental state and arousal of the experimental subjects during the period of the study.

Methods

Subjects

Ten volunteers, five of whom were female, took part in the study. They were all university students aged 20-30 years, who were physically fit and who were shown to have normal haematology and on

biochemical profile had normal renal and hepatic function.

They underwent personality (Eysenck Personality Inventory—Eysenck & Eysenck, 1964) and psychiatric screening (Middlesex Hospital Questionnaire—Crown & Crisp, 1966). Their scores on these tests were compared with the norms for Birmingham University students, and they were shown to be within the normal range for that population.

Plan of the study

Each subject attended twice having fasted overnight and on one occasion received an oral dose of trazodone (1 mg/kg) in solution and on the other was given an equally bitter-tasting placebo. The order of administration was random and neither the participants nor the experimenters knew when they were receiving the active preparation. Apart from the nature of the substance administered, the study on the two occasions was identical.

Plasma levels

Blood samples were obtained from a cannula inserted into a forearm vein every 10 min for the first half hour, every 15 min for the next 45 min and then half hourly up to 6 hours. The cannula

was then removed and the subjects were allowed to get up. A final 24 h sample was taken by venepuncture.

The samples were analysed by a g.l.c. method in which methyl trazodone (1-(4-phenyl, 1 piperazinyl) propyl, 3-methyl, 4-phenyl, 1, 2, 4-triazolo-5-one) was used as an internal marker. Aliquots of plasma to which the marker had been added were made alkaline and were then extracted with diethyl ether. The concentrated extract was injected on to a gas chromatograph fitted with a glass column (2 ft x $\frac{1}{4}$ in. o.d.) packed with 3% O.V.1 on gas chrom Q (Field Instruments), silanized with hexamethyldisilazane, and conditioned at a temperature of 260°C.

Heart rate

Heart rate was measured during the period of study by means of a Socially Acceptable Monitoring Instrument (S.A.M.I.) supplied by T.E.M. Sales Ltd, Crawley, Sussex.

The device is compact, easy to wear, and does not interfere with, and is not influenced by, vigorous activity. It uses reversible electrochemical integrators (known as E-cells) for storing data which derive their input signal from two adhesive chest electrodes using an isotonic agar liquid junction. The ECG signal thus detected is amplified and filtered by the circuits inside the S.A.M.I. and converted to a constant charge pulse which is applied to the E-cell. The circuits of the S.A.M.I. ensure a high degree of protection against muscle potential and interfering signals derived from the environment.

At the end of a period of measurement the E-cell is removed from the S.A.M.I. It is then reset in an E-cell replay machine, which provides a digital readout of the quantity of charge stored in the E-cells. This value, multiplied by a constant and then divided by the number of minutes that the E-cell has been in the S.A.M.I. gives the mean heart beat over that time.

Mean heart rate was recorded for a period (approximately 1 h) prior to the study ('pre-test'), over half hour periods throughout the first 6 h (i.e. until the subjects were allowed up and the intravenous cannulas were removed) then for the period 6-12 h and 12-24 h after the ingestion of the drug or placebo (whilst the subjects were pursuing normal activities at home and during sleep).

Mental state

Changes in mental state and arousal were measured by an 18 item 100 mm visual analogue scale. A visual analogue scale (conventionally of 100 mm in

length) is probably the best way of measuring changes in emotional state (either objectively or subjectively) particularly if changes are occurring rapidly or repeated measurements are needed (Aitken, 1969). The particular 18 item scale used (see Table 1 for the various parameters measured) has been developed by the Medical Research Council Applied Psychology Unit at Cambridge. It is designed to measure changes both in mood and arousal (Herbert, G., personal communication) and was therefore felt to be particularly applicable to the present study.

Subjects who had previously been instructed in the techniques were presented with forms before the start of the experiment ('pre-test') at the exact time of the ingestion of the drug or placebo (0 h) then at half hourly intervals for the first 6 h of the study, at 12 h and finally at 24 h after ingestion.

There were two parallel versions of the test form: both contained the same parameters but had a different order of presentation of some of the items to obviate response set, order effects or halo effects. Subjects were asked, to mark quickly with a vertical line whereabouts they felt their mental state fell between the two parameters at that moment. For example on the line,

Alert _____ Drowsy
subjects who felt awake put their vertical mark toward the end of the left-hand part of the line, those who felt sleepy would mark toward the end of the right-hand part of it whereas the middle would be marked by those neither particularly sleepy nor alert.

It has been shown that the same individuals mark these lines in a consistent fashion, although there is a wide variation between individuals in how far from the centre they allow themselves to move (however extreme the change in their mood): this individual variation is related to personality. For this reason analysis of the results of the test was carried out by non-parametric statistical techniques using an individual's difference scores, means and standard errors.

For each parameter at every test period a score was obtained by measuring the distance along the 100 mm line to the mark made by the subject. The significance of the differences between the results obtained after the placebo and after trazodone for each test period was obtained using the Wilcoxon matched-pairs signed-ranks test (Siegel, 1956).

Results

Plasma levels of trazodone

Figure 1 shows the plasma trazodone levels for the whole group expressed as means and standard

Figure 1 Mean plasma levels ($\pm$ s.e. mean) of trazodone obtained from ten subjects after an oral dose of 1 mg/kg.

errors. Although this appears as a smooth curve the group appeared to consist of two sub-groups as shown in Figure 2. Five subjects, three females and two males, had a high initial peak at 20-30 min and then a lesser peak at 1 h, whilst the others had a lower peak at 20-30 min and their major peak

occurred after 1 hour. The drug has a fairly long half life since easily detectable amounts were still present in the plasma 24 h after a single dose.

Heart rate

The effect of trazodone on the mean heart rate of subjects compared with placebo is shown in Figure 3. Some reduction in rate occurred after taking the placebo because the subjects were resting. However, when compared with placebo, trazodone caused a marked bradycardia which persisted after the subjects got up. Comparisons of mean heart rate for each of the fourteen test periods (trazodone v. placebo) showed a highly significant overall difference in that trazodone lowered heart rate compared with placebo ($P < 0.001$, Binomial test (Siegel, 1956).

A comparison of heart rate for each subject for each test period (14) for trazodone and placebo was made and the difference between the two was used in the Wilcoxon matched-pairs signed-ranks test (Siegel, 1956). A significant lowering of heart rate under trazodone occurred at 0-0.5 h ($P < 0.05$), 0.5-1 h ($P < 0.01$), 2.5-3 h ($P < 0.02$), 3-3.5 h ($P < 0.05$), 4-4.5 h ($P < 0.05$), 5-5.5 h ($P < 0.02$) and 12-24 h ($P < 0.02$).

The difference in heart rate between 12-24 h after trazodone compared with placebo was significant and surprising.

Figure 2 Individual plasma trazodone levels attained by two subjects after an oral dose of 1 mg/kg. (a) N.S.; (b) G.S.

Figure 3 A comparison of the effects of trazodone (1 mg/kg orally) (cross-hatched columns) and placebo (open columns) on heart rate (mean of ten subjects).

Mental changes

Table 1 shows that for 9 of the 18 parameters there were no significant differences between active v. placebo conditions. Four parameters (Alert-Drowsy; Attentive-Dreamy; Clear Headed-Muzzy; Well co-ordinated-Clumsy) were significantly affected by trazodone in that significant differences ($P < 0.05$ or better) occurred six or more times during the fourteen test periods for each particular parameter all in the direction of 'worsening' with trazodone (Table 2).

Five other parameters, as will be seen from Table 1, were somewhat affected by trazodone in that there was a consistent difference between the means obtained under trazodone and those obtained under placebo, but these differences reached statistical significance less than six times out of the 14 test periods (Table 2). Mean values (trazodone and placebo) for four parameters are depicted in Figure 4, three of these are significantly affected.

Figure 4 Examples of changes in visual analogue scale (VAS) scores of mental state produced by trazodone (1 mg/kg orally) (●) and placebo (○). (a) Clumsy—well co-ordinated 0-100; (b) muzzy—clear-headed 0-100; (c) sad—happy 0-100; (d) dreamy—attentive 0-100.

Table 1 Effect of trazodone on subjective feeling as measured by a visual analogue scale rating on word pairs.

No effect	Some effect	Significant effect
Happy	— Sad	— Lethargic*
Relaxed	— Tense	— Mentally slow*
Elated	— Depressed	— Withdrawn*
Contented	— Discontented	— Incompetent*
Outward going	— Self centred	— Feeble*
Bored	— Interested	—
Calm	— Excited	Alert
Tranquil	— Troubled	Attentive
Friendly	— Antagonistic	Clear-headed
		Well co-ordinated
		— Clumsy*

* Trazodone ingestion was associated with a shift toward this end of the 100 mm line.

Table 2 After trazodone at the times indicated the subjects felt significantly more

0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	3.5 h
Dreamy (0.025)	Dreamy (0.01)	Drowsy (0.01)	Dreamy (0.01)	Dreamy (0.02)	Dreamy (0.01)	Dreamy (0.025)
Drowsy (0.02)	Drowsy (0.02)	Mentally slow (0.05)	Drowsy (0.02)	Drowsy (0.01)	Muzzy (0.05)	Drowsy (0.01)
Mentally slow (0.05)	Lethargic (0.01)	Feeble (0.05)	Mentally slow (0.02)	Mentally slow (0.01)	Clumsy (0.01)	Mentally slow (0.01)
Lethargic (0.05)	Muzzy (0.05)	Clumsy (0.05)	Muzzy (0.05)	Lethargic (0.05)	Incompetent (0.01)	Incompetent (0.01)
Incompetent (0.05)			Clumsy (0.05)	Feeble (0.05)	Muzzy (0.05)	Muzzy (0.05)
Muzzy (0.01)				Muzzy (0.05)		Clumsy (0.02)
Clumsy (0.05)						
4 h	4.5 h	5 h	5.5 h	6 h	12 h	24 h
Mentally slow (0.05)	Dreamy (0.01)	Drowsy (0.05)	Incompetent (0.05)	Drowsy (0.05)	None	None
Feeble (0.025)	Drowsy (0.01)	Drowsy (0.05)	Muzzy (0.05)	Mentally slow (0.01)		
Incompetent (0.05)	Mentally slow (0.02)	Mentally slow (0.01)		Clumsy (0.01)		
Clumsy (0.05)		Incompetent (0.02)				
		Muzzy (0.01)				
		Clumsy (0.05)				

(Figures in parentheses are *P* values <)

Discussion

This study has shown that it is possible to measure the effect of a psychotropic drug while its pharmacokinetic properties are being evaluated. For this purpose a placebo preparation and the use of the subjects as their own controls is necessary and strictly a control period where subjects take neither drug nor placebo, but go through the same assessment procedure, should ideally be included.

These measures have shown that a single oral dose of trazodone in normal subjects has a significant effect on arousal but not on mood, being neither euphoriant nor anxiolytic. The antidepressant effects of a drug can only be tested in a depressed population and even in such a population a single dose study would be totally inadequate. However, we investigated trazodone's effect on mood in normal subjects as it is important to distinguish a potential antidepressant drug from a simple euphoriant, which would be clinically ineffective in relieving depression and might lead to abuse. Trazodone was not euphoriant and in this single dose study its effects were similar to those we would probably have obtained from a tricyclic antidepressant.

The effect of trazodone on heart rate was surprising. The bradycardia apparently produced

by the drug may have been due either to a direct effect on the heart or an indirect effect arising from the drug's action at the central nervous system. An alternative but unlikely explanation for the effect of the drug on arousal is that the effects on the heart were primary and the mental changes simply reflected a reduction in cerebral perfusion. However there were no clinical features such as pallor or sweating to suggest a reduced cardiac output. These observations merit further investigation and it would be of interest to know if a single dose of a tricyclic antidepressant had a similar effect.

This study has demonstrated that there was little direct relationship between blood levels of the drug and its psychotropic effect, although there was a tendency for effects to be maximal in the first hour. Since, however, it is presumably brain level of the drug rather than blood level that produces effects on arousal this is not too surprising.

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