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BLOOD LEVEL STUDIES WITH VILOXAZINE HYDROCHLORIDE IN MAN

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1 The pharmacokinetic characteristics of a new antidepressant, viloxazine hydrochloride, (ICI 58,834, Vivalan), have been investigated in four separate studies.

2 In Study 1, blood levels were measured over a period of 24 h after single doses of viloxazine hydrochloride from 10-100 mg (expressed as base). In Study 2, blood levels were measured over 24 h, during which three single doses of viloxazine hydrochloride (80 mg, expressed as base) were given 4 h apart. In Study 3, blood samples and urine and faeces were collected for 96 h after doses of 40 and 100 mg of [^{14}C] viloxazine hydrochloride (40 μCi). In Study 4, 1 h blood levels were measured at weekly intervals during a comparative clinical trial in which viloxazine was given at a dose of 100 mg four times a day.

3 The half-life of the drug is in the range 2-5 h with maximum blood levels occurring in 1-4 h of the oral dose. Maximum blood levels are proportional to the oral dose given over the range studied (0.76(μg/ml)/(mg/kg)). The drug is very well absorbed orally, only 2% being found in faeces. Repeated dosing at 4 hourly intervals leads to slightly higher blood levels after the second, but not subsequent, doses. No accumulation was seen from week to week in depressed patients. No regular sex difference was seen in the pharmacokinetic characteristics of viloxazine hydrochloride but two females in one study did show a markedly higher maximum blood level and apparently longer half-life than the males.

4 It is concluded that viloxazine is rapidly and almost totally absorbed after an oral dose, and has a shorter half-life than the tricyclic antidepressants; therapy with it should be easily controllable.

Introduction

Viloxazine hydrochloride (ICI 58,834, 2-(2-ethoxyphenoxymethyl)-2,3,5,6,tetrahydro-1,4,oxazine, Vivalan) is a new antidepressant of novel chemical structure. Its animal pharmacology has been summarized by Mallion, Todd, Turner, Bainbridge, Greenwood, Madinaveitia, Somerville & Whittle (1972). Controlled studies against imipramine in depressed patients by Peet (1973), and Bayliss, Dewsbury, Donald, Harcup, Mayer, Million, Molla, Murphy, Plant & Shaoul (1974) and Tsegos & Ekdawi (1974) have shown that it has an antidepressant effect at least equal to that of imipramine. Viloxazine was found, however, to be the better tolerated drug with fewer side effects, especially anticholinergic ones, than imipramine. Kirby & Turner (1974) reported that peak blood levels of viloxazine in human volunteers were reached about 2 h after an oral dose, peak blood levels being of the order of 0.8 (μg/ml)/(mg/kg) dose and were similar to those predicted by Case (1973). Peet (1973) reported that he could not determine any relationship between blood levels and clinical effect in depressed patients.

This paper reports a variety of blood level studies that have been carried out with viloxazine hydrochloride in man.

Methods

Four separate studies are reported in this paper. All doses are expressed as free base.

Study 1

In this study sixteen volunteers took single doses of viloxazine hydrochloride from 10-100 mg on

forty-two separate occasions. There were twelve males with a mean age of 31.0 years (range 20-42 years) and a mean body weight of 74.1 kg (range 60.4-85.0 kg) and four females with a mean age of 24.5 years (range 21-28 years) and a mean body weight of 56.4 kg (range 47.7-61.5 kg). All subjects were considered to be fit and healthy, both physically and mentally, and gave informed consent. Single doses of viloxazine hydrochloride were administered as film coated tablets, either after a light breakfast or in the fasting state, and venous blood samples were taken for assay of drug levels at intervals up to 24 h afterwards.

Study 2

In this study four male volunteers took three single doses of viloxazine hydrochloride (80 mg) at 4 hourly intervals and venous blood samples were taken at intervals for 25.5 h thereafter. The mean age of the subjects was 29.3 years (range 20-42 years) and their mean body weight was 72.2 kg (range 60.4-81.7 kg). Again, the subjects were considered to be fit and healthy and gave informed consent.

Study 3

In this study two male volunteers (ages 37 years and 44 years, and body weight 95 kg and 102 kg, respectively) each took two doses of [^{14}C] viloxazine hydrochloride (40 μCi) on two occasions 6 weeks apart. The volunteers took 40 mg radiolabelled viloxazine hydrochloride on the first occasion and 100 mg on the second, and blood samples, urine and faeces were collected for 96 hours. Again, the subjects were judged to be fit and healthy and gave informed consent. The radiolabelled viloxazine was administered in hard gelatine capsules.

Study 4

In this study venous blood samples were taken from depressed patients who were being given viloxazine hydrochloride at a dose of 100 mg four times a day in a comparative clinical trial that has been reported elsewhere by Peet (1973). Blood samples were taken 1 h after the first dose of the day on days 1, 7, 14 and 21 in thirteen patients. There were twelve females and one male. The mean age of the group was 60.4 years (range 41-74 years) and mean body weight on admission 55 kg (range 40.5-65.8 kg).

Assay methods

Blood levels of viloxazine were determined by gas liquid chromatography of the heptafluorobutyrate derivative, a specific method described elsewhere by Case (1973). Average recovery from blood was 85% (± 6.5) and the minimum detectable level was 0.02 μg/ml blood.

Blood, urine and faeces from the radiolabelled study were assayed by conventional methods and the results are reported elsewhere by Case & Reeves (1974).

Results

The mean blood level curves for each dose level used in Study 1 are shown for males in Figure 1 and for females in Figure 2. From these results a variety of pharmacokinetic data may be derived.

Half-life

The blood half-life of viloxazine was determined from the data obtained in Study 1 and was in the range 2-5 h, the most reliable measurements being in the range 2-3 hours. In Study 3 the half-life of radioactivity in blood was in the range 5-6 h while in the same study the half-life of viloxazine itself was 4 hours. This small difference in half-life is due to the presence of metabolic products in blood not detected by the chemical method of assay, and is discussed elsewhere by Case & Reeves (1974).

Maximum blood levels

Table 1 shows the maximum mean blood level achieved at each dose level used in Study 1, together with the time at which it occurred. Linear regression of the data adjusted for body weight gives a maximum blood level of 0.76(μg/ml)/(mg/kg) dose.

Absorption

The time of maximum blood levels seen in Studies 1 and 2 was in the range 1-4 h (mean 2.3 hours). In those instances where viloxazine hydrochloride was taken in the fasting state the time of maximum blood level was at 1 h in 9 out of 10 observations, whereas when taken after a light breakfast much greater variation was seen. In Study 3 no more than a total 2% of the radiolabelled dose was found in faeces in the period 0-72 h, showing almost complete absorption of the drug. In this study, blood levels attained were consistent with those seen in other studies where tablets were used.

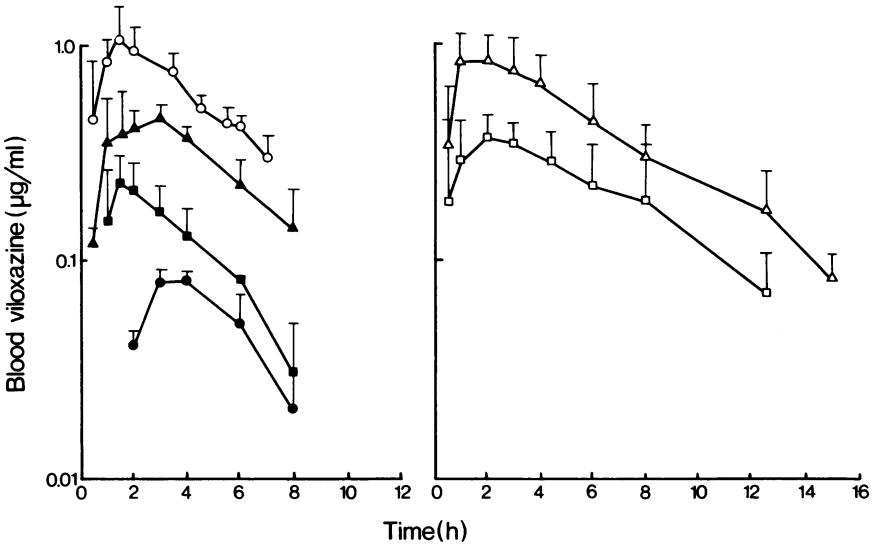

Figure 1 Mean blood level curves (±s.d.) for single doses of viloxazine hydrochloride (●, 10 mg $n = 2$; ■, 20 mg $n = 2$; ▲, 40 mg $n = 2$; ○, 80 mg $n = 4$; □, 50 mg $n = 5$; △, 100 mg $n = 19$, expressed as base) in twelve male volunteers from thirty-four observations.

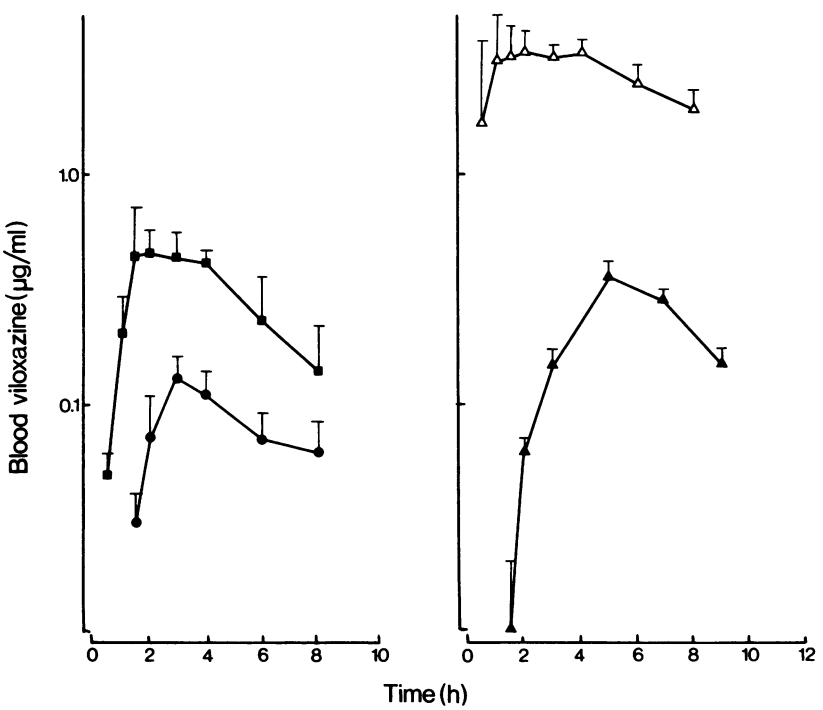

Figure 2 Mean blood level curves (± s.d.) for single doses of viloxazine hydrochloride (●, 10 mg $n = 2$; ■, 20 mg $n = 2$; ▲, 40 mg $n = 2$; △, 100 mg $n = 2$ expressed as base) in four female volunteers from eight observations.

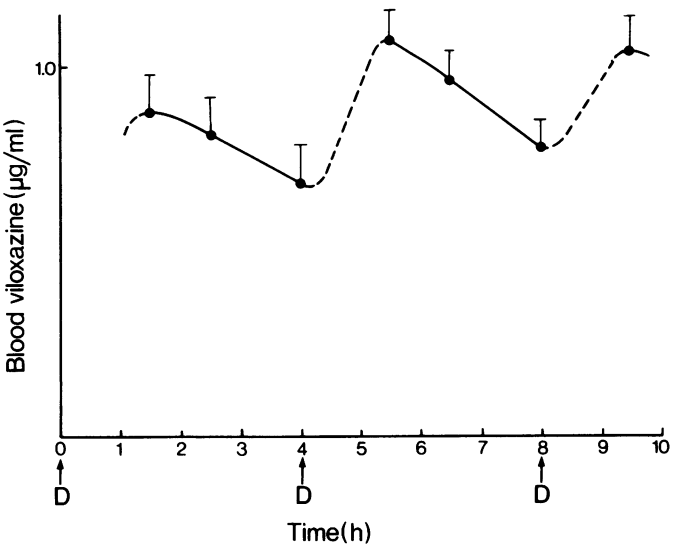

Figure 3 Mean blood level curve (± s.d.) from four male volunteers over a 9 h period during which three single doses of viloxazine hydrochloride (80 mg expressed as base) were taken at 4 hourly intervals. 'D' indicates time of dosing.

Effect of repeated dosing

Figure 3 shows the mean blood level curve seen in Study 2. This blood level profile is of the order predicted by the half-lives measured in Study 1. As expected, a small increase in the maximum blood level occurred after the second dose but accumulation following the third dose was minimal. At the end of 25.5 h no drug could be detected in the blood.

Table 2 shows the mean 1 h blood levels from Study 4 in patients on days 1, 7, 14 and 21. Because these are single point estimations at 1 h and the time of the peak blood level varies in the range 1-4 h (above), it is difficult to compare the mean levels at each week. It appears that the 1 h blood level after the first (in effect, single) dose of viloxazine is lower than that seen after 7 and 14 days of treatment but similar to that on day 21. However, due to the small numbers used and the variations seen, none of these differences reach statistical significance ($P < 0.1$, > 0.05). Peet (1973) has reported that no relationship could be shown between blood level and clinical effect, although the sample was small and involved a fixed dose level. However, the mean 1 h blood level in responders (1.0 μg/ml) was higher than in non-responders (0.65 μg/ml).

Table 1 Maximum mean blood level (μg/ml) of viloxazine, and the time (h) of achieving maximum mean blood level in twelve males and four females who took single doses of viloxazine hydrochloride between 10 and 100 mg (dose expressed as base).

Oral dose (mg)	10		20		40		50		80		100	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Maximum mean blood level (μg/ml)	0.08	0.13	0.23	0.46	0.46	0.36	0.37	–	1.02	–	0.83	3.56
Time of maximum mean blood level (h)	3.5	3	1.5	2	3	4	2*	–	1.5	–	1.5*	2
Number of observations	2	2	2	2	2	2	5	–	4	–	19	2

* Tablets taken on empty stomach

Table 2 Mean 1 h blood level of viloxazine (μg/ml ± s.d.) on the 1st, 7th, 14th and 21st days of treatment with viloxazine hydrochloride (100 mg four times a day, dose expressed as base) in thirteen depressed patients.

Day number	1	7	14	21
Mean blood level (μg/ml)	0.62	1.26	1.33	0.56
± s.d.	0.50	0.15	1.36	0.63

Possible sex differences

Study 1 included four females who each took two single doses of viloxazine of 10, 20, 40 or 100 mg. Table 3 shows the mean maximum blood level, time of maximum level, half-life and area under the curve adjusted for dose and body weight for these four dose levels divided by sex.

It can be seen that, whilst at the dose level of 10 and 40 mg there was little sex difference, at the 20 and 100 mg doses there was a clear difference with the females having higher maximum blood levels, with a longer mean half-life and a greater mean area under the curve. No difference could be found between the two females taking the 10 and 40 mg doses and the two taking the 20 and 100 mg doses that could account for these differences.

In Study 4 all but one of the thirteen patients were females and the mean 1 h blood level in this group was similar to that seen in males taking 100 mg single doses in Study 1. The higher blood levels seen in two females in Study 1 is clearly not due to better absorption. This is because Study 3 showed viloxazine hydrochloride to be totally absorbed and to produce blood levels in that study consistent with those attained by the two females in Study 1 who did not show elevated levels.

Discussion

The pharmacokinetic characteristics of a drug must be considered in relation to its area of clinical use, in this case as an antidepressant. Viloxazine hydrochloride is rapidly and almost completely absorbed with maximum blood levels occurring within 1-4 h of an oral dose. Thus, as far as therapy is concerned, poor absorption of the drug should not prove a problem. It is, however, seen that absorption is faster and more reproducible when the drug is taken on an empty stomach, although the difference is unlikely to be of clinical significance. Viloxazine has a shorter half-life than the tricyclic antidepressants and in the studies described the half-life was found to be 2-5 hours. Therefore, the accumulation of the drug in blood during the day on a two, three or four times a day regime of dosing will not be considerable and no significant accumulation will occur from day to day. Again, this contrasts with the tricyclic antidepressants (Glassman & Perel, 1973). The maximum blood level is proportional to the oral dose given over the range studied (10-100 mg) being in the order of 0.76(μg/ml)/(mg/kg) and this is similar to the figure of 0.8(μg/ml)/(mg/kg) calculated by Kirby & Turner (1974), and predicted by Case (1973).

No regular difference in the pharmacokinetic profile of viloxazine between males and females

Table 3 Mean maximum blood level of viloxazine (μg/ml), mean time of maximum blood level (h), mean half-life (h) and area under curve (mg^{-1} kg^{-1}) in four males and four females at single doses of viloxazine hydrochloride (10—100 mg, dose expressed as base).

Dose (mg)	*Sex*	*Number of observations*	*Mean maximum blood level (μg/ml)*	*Mean time of maximum level (h)*	*Mean half-life (h)*	*Area under curve (mg^{-1} kg^{-1})*
10	M	2	0.12	2.5	2.7	2.83
	F	2	0.14	3.0	2.4	3.24
20	M	2	0.23	1.5	2.7	3.22
	F	2	0.54	2.75	3.8	6.1
40	M	2	0.54	2.25	2.8	3.69
	F	2	0.30	4.0	3.2	2.1
100	M	2	1.13	1.75	2.3	4.46
	F	2	4.12	2.25	4.6	11.33

has been seen, although two of the female volunteers achieved blood levels of viloxazine markedly higher than the males taking the same doses in the same study. No reason for this was found and it is noted that the mean 1 h blood level seen in twelve female depressed patients was of the same order as the mean 1 h blood level seen in male volunteers taking the same unit dose (100 mg). No significant accumulation of viloxazine blood levels was seen in the patients taking the drug over a 3 week period, although mean blood levels on days 7 and 14 appeared higher than on days 1 and 21. If further work should show that these are real differences there is no obvious pharmacokinetic explanation for them revealed by the present studies. No statistically significant relationship between clinical effect and blood levels was detected although the sample was small and involved only one dose level with a small range of blood levels. In spite of this, the mean 1 h blood level was numerically higher in responders than in non-responders. Further work in this area may, therefore, demonstrate a relationship.

The data obtained in the studies described indicate that viloxazine is virtually completely absorbed, produces blood levels proportional to dose, has a short half-life and is rapidly eliminated from the body via kidney. It may, therefore, be concluded that therapy with the drug should be easily controllable and that, on cessation of the drug, it will be rapidly cleared from the blood. This may be an advantage in the treatment of potentially suicidal patients.

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