and early afternoon.⁴ As suicide and attempted suicide have different psychological causes and epidemiological risk factors, these data support the hypothesis that chronobiologically determined changes influence suicidal behaviour. The acrophases of important biological variables such as temperature, heart rate, and cortisol secretion vary in people with affective disorders compared with control subjects and may affect behaviour in addition to diurnal changes in mood and social activities. Increased adrenergic activity and lowered serotonergic activity⁵ in the afternoon might play a part in mood changes.

It could also be argued, however, that people who attempt suicide by minor self poisoning often do not want to die and their cry for help is more likely to be heard in the hours of the day when social and psychiatric services are available.

In conclusion, a specific temporal risk, defined as the point of confluence of many factors (hormonal, environmental, and behavioural), probably plays a part in suicidal behaviour. Treatment of depressive disorders might therefore be improved by aiming for peak drug concentrations at vulnerable times.

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Postural hypotension in elderly patients given carvedilol

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First dose postural hypotension is commonly observed with antihypertensive drugs,^{1,2} but its incidence may be overstated in clinical trials because of protocol requirements, which may include frequent venesection, fasting, acute withdrawal from caffeine, and frequent changes in posture.¹ The β blocker vasodilator drug carvedilol is associated with orthostatic hypotension, particularly in elderly people.²⁻⁴ We assessed the incidence of first dose hypotension in the absence of possible confounding factors linked to protocol.

Methods and results

The study group comprised 16 elderly patients (nine men; mean (SD) age 70 (6), mean weight 73 (17) kg) with uncomplicated mild or moderate hypertension whose supine diastolic blood pressures were 90-110 mm Hg after one week's washout with placebo after antihypertensive treatment. Previous studies showed that a sample of 10-18 subjects would produce an 80% chance of detecting a difference in response of 10 mm Hg between treatments at the 95% confidence level. The protocol was approved by the Austin Hospital Ethics Committee, and consent obtained from each patient.

The study was a randomised double blind crossover design with four study days with single doses—carvedilol 12.5 mg, carvedilol 25 mg, pindolol 15 mg, and placebo—each separated by a washout of ≥ 7 days. The patients were randomly allocated to eight different sequences of treatment.

After sitting for 10 minutes the patients received their allocated treatment and a standard breakfast. They then sat for an hour, walked about during the second hour, and were supine during the third hour. Blood pressure and heart rate were recorded with patients sitting (supine during the third hour) then after one minute standing, at 0, 30, 60, 125, and 180 minutes after they had received the treatment.

The main outcome measures were Δ supine blood pressure (blood pressure at time₀—blood pressure at time_i) and Δ standing blood pressure (standing blood pressure at time_i—supine blood pressure at time_i), where time_i was the time that the measurement was taken and time₀ the value at baseline. These variables were analysed with three way analysis of variance, with patient, treatment, and period of study as factors, and treatment differences were estimated.⁵

Although all patients receiving placebo and pindolol could stand at all time points, two patients receiving carvedilol 25 mg could not stand at 125 minutes and two others receiving carvedilol 25 mg could not stand at either 60 or 125 minutes. Of these four patients, one could not stand at 125 minutes and another could not stand at either 60 or 125 minutes when they received carvedilol 12.5 mg. The table summarises differences between treatments in Δ supine blood pressure and Δ standing blood pressure two hours after each drug was given: carvedilol produced a dose dependent fall in supine blood pressure when compared with the placebo. Carvedilol 25 mg and pindolol produced similar reductions in supine blood pressure with minimal treatment differences. Dose dependent postural falls in standing blood pressure occurred with carvedilol. This orthostatic response was significantly greater with carvedilol 25 mg than with pindolol despite similar reductions in supine blood pressure.

Comment

The incidence of first dose postural hypotension has been reported in pharmacokinetic studies as being as high as 40% with carvedilol.^{2,4} To avoid potential aggravating factors we did not take blood samples, the patients received their drugs with food, and each patient began the study seated.

Despite these precautions some patients could not stand after a single dose of carvedilol, and all patients had significantly greater falls in systolic and diastolic blood pressure in the standing position with carvedilol 25 mg than with the placebo, carvedilol 12.5 mg, and pindolol. Symptoms were obvious 60 and 125 minutes after carvedilol had been given, corresponding to the times of maximum hypotensive response to carvedilol (at 1-2 h).³ No symptoms of postural effects occurred, however, with pindolol.

Estimated mean differences* (95% confidence interval) in Δ supine blood pressure and Δ standing blood pressure between treatments two hours after they had been given to 16 elderly patients

	Systolic		Diastolic	
	Difference in blood pressure (mm Hg)	P value	Difference in blood pressure (mm Hg)	P value
Δ Supine blood pressure:				
Carvedilol 12.5 mg v placebo	17.2 (8.8 to 25.6)	<0.001	3.6 (-2.4 to 9.5)	0.233
Carvedilol 25 mg v placebo	22.0 (13.7 to 30.3)	<0.001	9.4 (3.5 to 15.2)	0.003
Carvedilol 25 mg v 12.5 mg	4.9 (-3.5 to 13.3)	0.246	5.8 (-0.1 to 11.7)	0.055
Carvedilol 25 mg v pindolol 15 mg	1.8 (-6.8 to 10.4)	0.668	0.3 (-5.8 to 6.3)	0.922
Δ Standing blood pressure†:				
Carvedilol 12.5 mg v placebo	4.6 (-8.7 to 17.9)	0.489	7.3 (0.4 to 14.2)	0.038
Carvedilol 25 mg v placebo	20.4 (7.3 to 33.5)	0.003	14.9 (8.1 to 21.7)	<0.001
Carvedilol 25 mg v 12.5 mg	15.9 (2.7 to 29.1)	0.020	7.5 (0.7 to 14.4)	0.003
Carvedilol 25 mg v pindolol 15 mg	22.0 (8.5 to 33.5)	0.002	10.1 (3.1 to 17.2)	0.006

*Determined with the SAS statistical package.

†In subjects unable to stand, standing blood pressure was assumed to be 65/45 mm Hg.

Recommendations on dose for managing hypertension suggest starting with carvedilol 12.5 mg daily, with subsequent increases to achieve control of the blood pressure. On the basis of our results, however, a lower starting dose may be needed in elderly hypertensive patients to avoid first dose postural symptoms. Similar caution is probably necessary in other groups of patients likely to be sensitive to combined α β blockade—namely, those taking diuretic drugs or in heart failure.

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Informed consent to undergo serum screening for Down's syndrome: the gap between policy and practice

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See article on p 769 and editorial by Vyas

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The funding of antenatal screening programmes for Down's syndrome often emphasises laboratory aspects of the tests to the neglect of the counselling components. It is widely agreed that the decision about whether to undergo prenatal screening should be made by the pregnant woman on the basis of good information.¹ The high uptake of screening in some hospitals has brought into question the adequacy of information given about the tests before women undergo them.² To make informed decisions about whether to undergo testing women need to know what conditions the test might detect as well as the implications of negative and positive results. Such information may also be of benefit in preparing women for possible adverse outcomes of screening.³

We assessed knowledge about different aspects of serum screening for Down's syndrome in women being offered such tests. This provides an index of how well the counselling aspect of the programmes is being conducted.

Subjects, methods and results

The study subjects comprised 353 pregnant women of up to 18 weeks' gestation who attended one of five hospitals in the United Kingdom that currently offers routine serum screening for Down's syndrome. They provided baseline data as part of an intervention study to improve the communication skills, and ability to give information, of midwives and obstetricians.⁴

Proportions of women knowing about aspects of screening for Down's syndrome

Information about test	No (%) of women with correct knowledge (n=353)	Variance predicted by patient demographic variables (%)
Test is offered to all women	262 (74)	11
Test is performed at 16-18 weeks of pregnancy	314 (89)	14
Maternal blood sample is used for test	254 (72)	18
Test screens for Down's syndrome	134 (38)	5
Results take 1-2 weeks to come back	142 (40)	5
About 5% (1 in 20) women are recalled	45 (13)	4
Further tests are offered if result is positive	238 (67)	15
Most women with positive results have normal babies	112 (32)	3
Negative results do not guarantee that everything is alright with baby	127 (36)	12

Women completed questionnaires after a consultation with either a midwife or an obstetrician; during the consultation routine antenatal screening tests, including serum screening for Down's syndrome, were offered. Their knowledge was assessed by using a multiple choice questionnaire with nine items. The internal reliability of the questionnaire was measured by using Cronbach's α , which gave a coefficient of 0.66.

The amount of variance in knowledge predicted by demographic variables was assessed by performing discriminant function analyses for each item of the questionnaire. The demographic variables were age, number of children, socioeconomic class, and ethnicity. The table shows the proportions of women giving correct responses to the nine items and the variance predicted by the demographic variables.

Comment

Though women in this sample were knowledgeable about practical aspects of undergoing the test, they were less well informed about aspects of the test that could inform their decisions about whether to undergo testing and prepare them for possible adverse outcomes such as being recalled with a high risk result or giving birth to an affected child after a result indicating low risk.

The demographic variables were weak predictors of the variance in knowledge, particularly items on which fewer than half the women gave the correct answer. The pattern of women's knowledge reflects the observed emphasis of midwives and obstetricians when routinely informing women about prenatal screening⁵: information about the practical aspects of the test is emphasised, whereas information about the likelihood and implications of possible results is rarely given.

These results highlight the extent to which prenatal screening programmes are falling short of the counselling standards that have been set.¹ In addition to the setting of guidelines, effective staff training is needed to teach health professionals how to present prenatal screening tests in ways that will lead to informed decision making by patients.⁴

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