Influence of human insulin on symptoms and awareness of hypoglycaemia: a randomised double blind crossover trial

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Abstract

Objective—To investigate the apparent increased risk of severe hypoglycaemia associated with use of human insulin by comparing the pattern of symptoms of hypoglycaemia with human insulin and porcine insulin.

Design—Randomised controlled double blind crossover trial of treatment with human insulin and porcine insulin, with two treatment periods of six weeks.

Setting—Diabetes outpatient department of a university teaching hospital in Berne, Switzerland.

Patients—44 patients (25 men, 19 women) aged 14 to 60 years, with insulin dependent diabetes mellitus. All patients met the following criteria: receiving treatment with fast acting soluble insulin and long acting protamine insulin; performing multiple daily fingerstick blood glucose self measurements; and had stable glycaemic control with about one mild hypoglycaemic episode a week during the preceding two months.

Intervention—Patients were randomised to receive either human or porcine insulin for six weeks and were then changed over to the other type of insulin for a further six weeks.

Main outcome measure—Questionnaire recording "autonomic" and "neuroglycopenic" symptoms that occurred during hypoglycaemic episodes confirmed by a blood glucose concentration ≤2·8 mmol/l.

Results—Insulin doses and blood glucose, glycated haemoglobin A_{1c}, and fructosamine concentrations were similar during the two treatment periods. 493 questionnaires on hypoglycaemia (234 during treatment with human insulin and 259 during treatment with porcine insulin) were analysed. With human insulin patients were more likely to report lack of concentration (52% *v* 35%, p=0·0003) and restlessness (53% *v* 45%, p=0·004) and less likely to report hunger (33% *v* 42%, p=0·016) than during treatment with porcine insulin. The difference in the pattern of symptoms during the two treatments was similar to that between the 12 patients with a history of recurrent hypoglycaemic coma and the 32 patients without such a history.

Conclusions—The pattern of symptoms associated with human insulin could impair patients' ability to take appropriate steps to avoid severe hypoglycaemia. Caution should be exercised when transferring patients from animal insulin to human insulin, and a large scale randomised trial of the two types of insulin may be justified.

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Introduction

Decreased awareness of hypoglycaemia in diabetic patients transferred to treatment with human insulin was first reported in 1987 on the basis of retrospective questionnaire surveys.[1,2] Subsequently, in a randomised double blind crossover trial, hunger and sweating were found to be significantly less common initial symptoms of hypoglycaemia when human insulin, as compared with porcine insulin, was being taken.[3] Hunger and sweating were considered to be "warning symptoms"—that is, symptoms likely to alert the patients to their incipient hypoglycaemia and allow then to take evasive action. Conversely, a group of neuroglycopenic symptoms, including lack of concentration and confusion, were seen significantly more often as the initial symptoms of hypoglycaemia with human insulin. The authors suggested that the congnitive impairment associated with these symptoms could result in patients failing to take appropriate steps to avoid the development of hypoglycaemia. Their study was criticised, however, because the results were deemed to depend on the allocation of symptoms into the categories "warning" and "neuroglycopenic."[4]

In the hospital based case-control study reported in this issue (p 617) we found an increased rate of presentation for hypoglycaemia in patients transferred to human insulin.[5] In the present paper we report a randomised double blind study carried out to investigate whether transfer to human insulin leads to patients experiencing hypoglycaemia in a way that may hinder appropriate response.

Patients and methods

PATIENTS

Forty four outpatients were selected who met the following criteria: had insulin dependent diabetes mellitus confirmed by a C peptide concentration <0·03 nmol/l; were receiving treatment with fast acting soluble insulin and long acting protamine insulin; were performing routine multiple daily fingerstick blood glucose self measurements before the study; and had stable glycaemic control with about one mild hypoglycaemic episode a week during the preceding two months.

At the time of entry into the study 18 patients were being treated with human insulin and 26 with porcine insulin. Thirty one patients were taking four daily injections with a pen injector before meals. The remaining patients were taking two daily injections. Twelve patients had experienced recurrent hypoglycaemic coma, defined as two or more episodes during the preceding three years. Written informed consent was obtained from each participant, and the trial was approved by the ethical committee of the medical faculty of the University of Berne.

STUDY DESIGN

Twenty two of the patients were selected by using random number tables initially to receive human insulin; the remaining 22 patients initially received porcine insulin. The trial lasted for 12 weeks, with crossover to the other type of insulin after six weeks. Blind labelling of insulin was done by the hospital pharmacy staff. The semisynthetic human insulin and highly purified porcine insulins used were Insulatard (a protamine insulin, Nordisk) and Velosulin (a soluble insulin, Nordisk) (all 100 units/ml). The 31 patients using pen injectors used the same Insuject R (Nordisk) device during both study periods.

Fructosamine concentration (measured with the nitroblue tetrazolium test (Roche), reference value 1·5 mmol/l to 2·4 mmol/l) and glycated haemoglobin

concentration (measured with Hba1c Biorad, reference value 3·4% to 6·1%) were detemined at entry, crossover, and the end of the study. Fingerstick blood glucose measurements were performed three or four times daily—before meals and at bedtime. All patients used the same pen-sized ExacTech blood glucose meter. This device has been shown to produce reliable (interassay coefficient of variation 3·3% to 6·3%) and precise results.[6] The result is displayed after 30 seconds. When blood glucose concentration is below 2·2 mmol/l the meter displays "low" and when above 22 mmol/l displays "high." The meter was calibrated by the patient according to the manufacturer's instructions after every 10 measurements.

Hypoglycaemia was defined as a blood glucose value ≤2·8 mmol/l. Patients were asked to measure blood glucose concentration before ingestion of carbohydrates whenever possible. After recovery from hypoglycaemia the patients completed a standardised questionnaire. As main outcome measures the occurrence of eight major hypoglycaemic symptoms was assessed: sweating, tremor, hunger, restlessness, lack of concentration, confusion, visual disturbance, and aggressiveness.[7] Aggressiveness was infrequently reported (on only 3% of all reports) and was not analysed further. Cardiovascular autonomic function was investigated by measuring blood pressure and heart rate response on standing and by beat to beat variation in heart rate during one minute of deep breathing.[8] Tests were performed after the patient had abstained for 12 hours from tobacco, alcohol, and drugs containing sodium salicylate. A fall in systolic blood pressure of 30 mm Hg or more on standing was considered abnormal. Age dependent normal values were used for evaluation of the heart rate test results.[9]

DATA ANALYSIS

Data were analysed, both by episodes and by patients, before the coding of insulin type was broken. The analysis by questionnaire gives more weight to patients with a large number of episodes. It is, however, justified from a clinical point of view because every episode of hypoglycaemia represents a potential threat of death. In the analysis by questionnaire the frequencies with which symptoms appeared on the questionnaires during treatment with human insulin and with porcine insulin were investigated by using χ^2 tests with Yates's correction. In the analysis by patients frequencies of symptoms were calculated for each patient and treatment period as the number of occurrences of a given symptom divided by the total number of episodes of hypoglycaemia recorded by the patient. Within patient comparisons of the occurrence of each symptom when treated with human insulin and porcine insulin were performed by using Wilcoxon signed rank tests.

Because it is debatable how symptoms should be allocated to the categories autonomic and neuroglycopenic crosstabulations of all possible pairs of symptoms were performed and odds ratios calculated as a measure of the degree of association. Principal components analysis of questionnaire reponses was also performed.[10] This technique examines the propensity for different symptoms to be reported together. Logistic regression analysis[11] was used to investigate the probabilities of neuroglycopenic and autonomic symptoms being reported with human or porcine insulin. The possibility of treatment period interactions was examined.[12] Possible carryover effects were investigated by excluding the first week and the first two weeks of each treatment period. Paired *t* tests were used for within patient comparisons of blood measurements and insulin doses. Between patient comparisons we performed by using analysis of variance and χ^2 tests with Yates's correction where appropriate. Data were expressed as means (standard deviations), medians (ranges), or proportions (number in numerator). The computer programs SAS-PC and EGRET were used.

Results

Twenty two patients had normal results to autonomic cardiovascular function tests (duration of diabetes 13·8 (8·4) years), 17 patients had one or more abnormal heart rate test result (duration of diabetes 16·7 (9·5) years), and five patients had both abnormal heart rate and blood pressure test results (duration of diabetes 25·6 (6·5) years; p=0·03 by analysis of variance). There were no significant differences in the baseline characteristics between patients who received human insulin first and those who received porcine insulin first (table I). The most notable difference relates to history of recurrent hypoglycaemic coma, with eight of the patients who received human insulin first having experienced recurrent hypoglycaemic coma as compared with four of those who received porcine insulin first (p=0·31).

TABLE I—*Patients' baseline characteristics*

	Patients who initially received human insulin (n=22)	Patients who initially received porcine insulin (n=22)
Mean (SD) age (years)	37·7 (10·6)	33·3 (9·6)
Sex (M/F)	11/11	14/8
Mean (SD) duration of diabetes (years)	17·4 (8·0)	15·2 (10·4)
Mean (SD) body mass index (kg/m²)	23·9 (2·7)	23·3 (2·0)
No of injections daily:		
Four (with pen injector)	16	15
Two	6	7
Mean (SD) fructosamine (mmol/l)	2·87 (0·32)	2·81 (0·26)
Mean (SD) haemoglobin A_{1c} (%)	7·22 (1·20)	7·35 (1·12)
No with history of recurrent hypoglycaemic coma	8	4
No with retinopathy:		
Non-proliferative	3	7
Proliferative	2	2
No with nephropathy (urinary albumin ≥250 mg/l)	3	2
No with autonomic dysfunction:		
Abnormal heart rate	7	10
Abnormal heart rate and blood pressure	2	3

A total of 12 582 blood glucose measurements were performed (6150 during treatment with human insulin and 6432 during treatment with porcine insulin). In all 11 932 were routine measurements performed either in the morning after fasting, before lunch or dinner, or at bedtime. Table II shows the mean blood glucose concentrations calculated from these routine measurements. There were no significant differences between the two treatment periods. Haemoglobin A_{1c} and fructosamine concentrations and insulin doses were similar during the two treatment periods.

Of 6150 blood glucose measurements performed during treatment with human insulin, 417 (6·8%) were ≤2·8 mmol/l as compared with 510 (7·9%) among 6432 values during treatment with porcine insulin (p=

TABLE II—*Mean (SD) blood glucose, haemoglobin A_{1c}, and fructosamine concentrations and insulin doses during treatment with human insulin and porcine insulin*

	Treatment with human insulin (n=44)	Treatment with porcine insulin (n=44)	p Value*
Blood glucose (mmol/l):			
Fasting	7·89 (2·1)	7·67 (2·3)	0·2
Noon	7·24 (1·9)	7·38 (2·1)	0·4
Before supper	8·65 (1·9)	8·35 (1·9)	0·1
Bedtime	7·95 (2·4)	7·79 (2·3)	0·3
Haemoglobin A_{1c} (%)	7·49 (1·1)	7·45 (0·8)	0·8
Fructosamine (mmol/l)	2·85 (0·4)	2·82 (0·3)	0·4
Insulin dose (U/day)	43·4 (13·9)	42·8 (13·3)	0·2

*Paired *t* test.

0·024). There were three episodes of hypoglycaemic coma, one during treatment with human insulin and two during treatment with porcine insulin.

QUESTIONNAIRES

A total of 673 questionnaires on hypoglycaemia were completed: 323 during treatment with human insulin and 350 during treatment with porcine insulin, with 89 (28%) and 91 (26%), respectively, being excluded from analysis because the corresponding blood glucose concentration was >2·8 mmol/l. In 17 (7·3%) instances with human insulin and in six (2·3%) instances with porcine insulin (p=0·020) no blood glucose measurement was performed because of abrupt onset of hypoglycaemia. In the analysis presented here these episodes were included, although excluding them did not materially alter the results. This report is therefore based on 493 questionnaires, of which 234 and 259 were completed during treatment with human insulin and porcine insulin respectively. The median (range) number of questionnaires completed by each patient was 9 (1-30) when taking human insulin and 11 (1-23) when taking porcine insulin. This corresponds to a significant difference in the reporting of episodes of hypoglycaemia (p=0·0001) in a within patient comparison by the Wilcoxon signed rank test.

GROUPS OF SYMPTOMS

A total of 1262 symptoms were reported, giving an average of 2·56 symptoms per episode of hypoglycaemia. Overall, tremor was the most commonly reported symptom (246 (50%) episodes) followed by restlessness (216 (44%) episodes), lack of concentration (213 (43%) episodes), sweating (191 (39%) episodes), hunger (159 (32%) episodes), confusion (124 (25%) episodes), and visual disturbance (113 (23%) episodes). The principal component analysis with a two component solution explained 45% of the variance and clearly differentiated two groups of symptons. Sweating, tremor, and hunger contributed strongly to the first component, corresponding to the category of symptoms which has been termed "autonomic." Lack of concentration, confusion, restlessness, and visual disturbance contributed strongly to the second component, constituting a group of those symptoms which have been termed "neuroglycopenic." The odds ratios from crosstabulations ranged from 1·7 to 4·5 for autonomic symptoms, from 1·4 to 5·3 for neuroglycopenic symptoms, but from 0·5 to 1·4 for crosstabulations between autonomic and neuroglycopenic symptoms. All odds ratios and the coefficients from the principal component analysis are available from the authors.

SYMPTOMS DURING TREATMENT

Table III gives the frequencies of symptoms recorded during treatment with human insulin and porcine insulin. In the analysis based on questionnaires there were statistically significant differences between the treatment for lack of concentration, confusion, and restlessness which were all more common during treatment with human insulin. The difference was most pronounced for lack of concentration, which was recorded in 123 (53%) episodes of hypoglycaemia with human insulin but only 90 (35%) episodes with porcine insulin (p<0·0001). Analysis of symptom frequencies by patients rather than by questionnaire confirmed the differences between the two types of insulin for lack of concentration, confusion, and restlessness. Furthermore, there was a trend toward fewer episodes of hunger, tremor, and sweating during treatment with human insulin. Analysed either way, lack of concentration, restlessness, and tremor were the three most commonly reported symptoms treatment with human insulin whereas tremor, sweating, and restlessness were the symptoms most commonly reported with porcine insulin.

TABLE III—*Frequences of symptoms recorded during treatment with human insulin and porcine insulin*

Symptom	Treatment with human insulin	Treatment with porcine insulin	p Value
	*Analysis by questionnaire**		
Sweating	37 (86)	41 (105)	0·44
Tremor	52 (121)	48 (125)	0·50
Hunger	32 (76)	32 (83)	0·99
Restlessness	50 (117)	38 (99)	0·011
Lack of concentration	53 (123)	35 (90)	<0·0001
Confusion	30 (71)	20 (53)	0·015
Visual disturbance	26 (61)	20 (52)	0·16
	Analysis by patients†		
Sweating	41 (34)	43 (39)	0·19
Tremor	47 (40)	51 (42)	0·43
Hunger	33 (38)	42 (41)	0·016
Restlessness	53 (39)	45 (41)	0·004
Lack of concentration	52 (39)	35 (38)	0·0003
Confusion	32 (37)	23 (33)	0·10
Visual disturbance	28 (36)	22 (33)	0·073

*Figures are percentages (numbers) of questionnaires reporting symptoms, Yates's corrected, χ^2 test.
†Figures are mean (SD) percentage occurrences of symptoms, Wilcoxon signed rank test.

Compared with an absence of neuroglycopenic symptoms the odds ratio obtained from logistic regression for one neuroglycopenic symptom with human insulin as compared with porcine insulin was 1·7 (95% confidence interval 1·03 to 2·7), for two neuroglycopenic symptoms 2·1 (1·3 to 3·5), for three 2·8 (1·5 to 5·3), and for four 3·9 (1·7 to 9·1). No such trend was evident for autonomic symptoms.

There were no significant treatment period interactions,[12] with probability values ranging from 0·24 for visual disturbance to 0·98 for tremor. Results were not materially altered when the first week or the first two weeks of each treatment period were excluded from analysis. Therefore, no important carryover effect was present.

AUTONOMIC FUNCTION AND GLYCAEMIC CONTROL

There was no significant influence of autonomic function on the total number of autonomic or neuroglycopenic symptoms. Tighter glycaemic control, however, as indicated by lower fructosamine concentrations, was associated with a greater number of neuroglycopenic symptoms (p=0·002 by analysis of variance), while the number of autonomic symptoms was similar.

RECURRENT SEVERE HYPOGLYCAEMIA

To investigate which symptoms may be helpful for recognition of hypoglycaemia and which may impair awareness the 12 patients who had had two or more episodes of hypoglycaemic coma during the preceding three years were compared with the remaining 32 patients. Table IV shows that patients with a history of recurrent hypoglycaemic coma were older and had a longer duration of diabetes, lower fructosamine and haemoglobin A_{1c} concentrations, and a higher prevalence of abnormal autonomic function test results. These differences were not significant except for the

TABLE IV—*Characteristics of patients with and without history of recurrent hypoglycaemic coma during preceding three years*

Characteristic	History of recurrent hypoglycaemic coma: Yes (n=12)	No (n=32)	p Value
Mean (SD) age (years)	38·5 (10·1)	34·4 (10·3)	0·24
Sex (M/F)	8/4	17/15	0·64
Mean (SD) duration of diabetes (years)	19·6 (9·0)	15·1 (9·8)	0·15
Mean (SD) fructosamine (mmol/l)	2·67 (0·22)	2·90 (0·29)	0·018
Mean (SD) haemoglobin A_{1c} (%)	6·90 (0·81)	7·43 (1·23)	0·18
No with autonomic dysfunction	9	13	0·09
No with retinopathy	4	10	0·99
No with nephropathy	2	3	0·64

fructosamine concentrations (p=0·018). There were considerable differences in the overall occurrences of symptoms calculated over both treatment periods between the two groups. In the analysis by questionnaires patients with a history of recurrent hypoglycaemia were less likely than patients without such a history to report sweating (31% *v* 41%, p=0·060), tremor (28% *v* 57%, p<0·0001), and hunger (16% *v* 37%, p<0·0001) and more likely to report lack of concentration (53% *v* 40%, p=0·012), confusion (39% *v* 21%, p=0·00014), and visual disturbance (32% *v* 20%, p=0·009). Similar differences were observed in the analysis by patients, although conventional significance was reached only for hunger.

The odds ratio for whether a hypoglycaemic episode was recorded by a patient with a history of recurrent coma was calculated. The ratio increased from 1·0 if no neuroglycopenic symptoms were present to 4·2 (95% confidence interval 1·7 to 10·2) if all four symptoms were present. Conversely, the odds ratio decreased with the number of autonomic symptoms reported from 1·0 for no autonomic symptom present to 0·1 (0·03 to 0·3) for all three symptoms present.

Discussion

The present study confirms the findings of other studies that comparable blood glucose profiles and glycaemic control are obtained with similar doses of human insulin and porcine insulin.[3,13-15] Our results, however, show that the pattern of symptoms of hypoglycaemia in insulin dependent diabetic patients is different with the two treatments. This difference was evident under double blind conditions in a large number of prospectively recorded hypoglycaemic episodes. The neuroglycopenic symptoms lack of concentration, confusion, and restlessness were experienced significantly more frequently when human insulin was being used. Lack of concentration was one of the most common symptoms with human insulin, but not with porcine insulin. Although autonomic symptoms were experienced less often with human insulin when analysed by patient than when analysed by questionnaire, the predominant finding of this study is the more frequent occurrence of neuroglycopenic symptoms with human insulin.

The allocation of symptoms into the categories "autonomic" and "neuroglycopenic" needs to be considered. An earlier study showing that neuroglycopenic symptoms were more common and autonomic symptoms less common with human insulin was criticised because restlessness was classified as a neuroglycopenic symptom.[4] It was argued that restlessness was a manifestation of autonomic stimulation. Because the differences observed between human and porcine insulin were no longer significant when this symptom was allocated to the autonomic category, the results were said to be inconclusive.[4] The allocation of hunger is also controversial. In one standard textbook hunger is classified as a neuroglycopenic symptom in one chapter[16] and as an autonomic symptom in another.[7] Other major textbooks consider hunger as an autonomic symptom and restlessness as a neuroglycopenic symptom.[17,18] This view is supported by the findings of the present study. Sweating, tremor, and hunger tended to occur together, suggesting that a common aetiology, probably stimulation of the autonomic nervous system, underlies them. On the other hand, lack of concentration, confusion, restlessness, and visual disturbance were associated, probably because neuroglycopenia plays a major part in their pathogenesis. The importance of the two categories of symptoms stems from the fact that neuroglycopenic symptoms are strongly associated with an increased risk of recurrent severe hypoglycaemia, and conversely, autonomic symptoms may protect against severe hypoglycaemia.

Does the pattern of symptoms observed with human insulin impair the recognition of hypoglycaemia, and is it therefore of concern from a clinical point of view? The incidence of hypoglycaemic coma (in one patient with human insulin and in two with porcine insulin) does not support this suggestion. This trial was not, however, designed to study the incidence of severe hypoglycaemia—a far greater sample size would be needed for that purpose.[19] Abrupt onset of hypoglycaemia was more common with human insulin, and significantly fewer hypoglycaemic episodes were recorded with human insulin, suggesting a less reliable recognition of hypoglycaemia. The strongest evidence that the pattern of symptoms with human insulin may be of concern, however, comes from the fact that neuroglycopenic symptoms were associated with a history of hypoglycaemic coma. In our case-control study we found that the risk of severe hypoglycaemia was indeed increased in patients transferred to human insulin during the period it was introduced into treatment.[5]

The differences betwen human insulin and porcine insulin may be of particular concern in patients with recurrent severe hypoglycaemia in whom a change to human insulin could exacerbate an existing tendency to neuroglycopenia. The factors associated with recurrent severe hypoglycaemia were longer duration of diabetes, higher prevalence of autonomic dysfunction, and tighter glycaemic control. Intensive insulin treatment leading to near normal blood glucose control is an established risk factor for severe hypoglycaemia.[20] The importance of autonomic neuropathy as an independent risk factor, however, has been questioned.[21]

The pathophysiological mechanism leading to the observed differences in the pattern of symptoms is unclear. Interestingly, the alterations produced by human insulin are similar to those which are observed in patients with tight glycaemic control. It has been shown that intensive treatment which reduces haemoglobin A_{1c} concentration may impair glucose counterregulation. The glucose concentration at which an adrenaline response occurs is lowered, its release is delayed, and hepatic glucose production is diminished.[22] In a study comparing symptoms in nine insulin dependent diabetic patients during hypoglycaemia induced by intravenous infusion of human or porcine insulin the first symptom occurred at a lower blood glucose concentration when human insulin was used.[23] While the threshold for adrenaline release in hypoglycaemia induced by human insulin as compared with in hypoglycaemia induced by porcine insulin has not been reported, several studies have investigated the magnitude of the catecholamine response to comparable hypoglycaemia induced by human or porcine insulin. In some studies decreased catecholamine responses were found with human insulin.[24,25] Others have not found such a difference,[26] and the issue remains controversial.[27] Counterregulation in response to hypoglycaemia may be triggered by a glucoregulatory centre in the hypothalamus.[21] Porcine insulin is more lipophilic than human insulin[28] and may therefore reach higher concentrations in brain tissue. The central activation of counterregulation might thus be modified by the type of insulin that induced hypoglycaemia. This hypothesis is supported by the recent finding that central neuronal function, as assessed by auditory evoked potentials, differs in human insulin induced hypoglycaemia and porcine insulin induced hypoglycaemia.[29]

In conclusion, treatment with human insulin is associated with a pattern of symptoms of hypoglycaemia which may increase the risk of severe hypoglycaemia.

Human insulin in general offers no advantage over highly purified animal insulins.[30] Patients should therefore be transferred to human insulin only when there is a medical indication, under a doctor's guidance, and after having been informed that a change in symptoms of hypoglycaemia could occur. As advocated previously,[31] a large randomised clinical trial is now needed to establish definitively whether there is an increased risk of severe hypoglycaemia associated with transfer to human insulin.

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Influence of posture and reference point on central venous pressure measurement

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Measurement of central venous pressure has been used as an indicator of the adequacy of transfusion for more than 20 years.[1,2] Despite the familiarity of the technique, there seems to have been little emphasis placed on the degree of variation in measurements caused by the patient's posture and the choice of reference point. Early reports emphasised the importance of measuring from the mid-axilla with the patient supine,[2] but this is not always practicable, particularly when patients are too breathless to tolerate lying flat. We determined the degree of variation in values for central venous pressure taken from two different reference points and with two different patient positions.

Patients, methods, and results

Twenty five patients who required monitoring of their central venous pressure had a standard 18 cm central venous cannula inserted by one of us (GH) through the right internal jugular vein. The cannula was connected to a bedside saline manometer, and free antegrade flow of saline and retrograde flow of blood was established by raising and lowering the reservoir. In all cases the column of saline fell rapidly on opening the tap to the patient and at the equilibration point the meniscus was observed to move with respiration. A mean value between the swings observed with respiration was recorded. Patients were asked to breathe as gently as possible while the recordings were being made. Four sets of readings were taken: (*a*) from the sternal angle with the patient's torso at 45°; (*b*) from the sternal angle with the patient lying flat; (*c*) from the mid-axillary line at the level of the fourth intercostal space with the patient lying at 45°; and (*d*) from the mid-axillary line at the level of the fourth intercostal space with the patient lying flat. In all cases readings

Central venous pressure measurements (cm H_2O) in 25 patients taken from sternal angle or mid-axilla and with patient at 45° or lying flat

Patient No	Age (years)	Central venous pressure (cm H_2O)			
		Sternal angle, 45°	Sternal angle, flat	Mid-axilla, 45°	Mid-axilla, flat
1	75	−13·0	−4·0	−1·0	3·5
2	45	−12·0	−3·0	0·0	4·0
3	28	−10·0	−1·5	−1·0	7·0
4	65	−9·0	−3·5	2·5	3·0
5	55	−8·5	−8·0	6·5	4·5
6	74	−8·0	−6·5	5·5	4·5
7	49	−6·5	−4·5	7·0	8·0
8	64	−6·0	−2·0	6·0	11·0
9	60	−5·0	−2·5	11·0	8·0
10	81	−5·0	−1·0	6·0	8·0
11	79	−4·0	0·0	3·0	12·0
12	80	−2·0	0·0	10·5	9·0
13	65	−2·0	3·5	13·5	14·0
14	65	−1·5	13·0	12·0	20·5
15	88	−0·5	4·5	11·5	14·0
16	51	0·0	8·0	14·0	17·0
17	67	0·0	1·0	10·0	10·0
18	76	0·0	0·0	7·0	6·0
19	75	1·0	3·5	17·5	12·5
20	36	1·0	3·0	12·0	14·5
21	50	6·5	14·0	23·0	24·5
22	79	7·5	11·5	20·0	22·5
23	78	8·5	10·0	18·5	21·5
24	74	8·5	8·5	23·5	19·0
25	71	9·5	17·5	24·5	27·0
Mean (SD)		−2·0 (6·5)	2·6 (6·8)	10·5 (7·5)	12·2 (7·1)
Variance		42·4	45·8	56·4	49·8