SKIN CONDUCTANCE RESPONSES TO AUDITORY STIMULI
AND ANTICIPATORY RESPONSES BEFORE VENEPUNCTURE IN
PATIENTS PREMEDICATED WITH DIAZEPAM OR MORPHINE

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SUMMARY
We have measured the skin conductance response to innocuous auditory stimuli and the anticipatory response before venepuncture in 45 patients receiving diazepam, morphine or no premedication before general anaesthesia. Subjective ratings of anxiety and sedation were measured using visual analogue scales. Skin conductance was less in subjects receiving diazepam than in the other groups, and the pattern of change of skin conductance in this group indicated superior adaptation to the environment during presentation of the innocuous stimuli compared with the other groups. After warning of venepuncture there was a large increase in skin conductance in all groups. There was a significant relationship between anxiety and skin conductance in unpremedicated patients and those receiving diazepam. (Br. J. Anaesth. 1993; 71: 512-516)

KEY WORDS
Premedication, diazepam, morphine.

Anxiety is an unpleasant emotional experience which is widespread in patients awaiting surgery. One of the aims of premedication is to reduce its intensity. Anxiety is a subjective concept and is most often measured by self-report. However, tests of emotional, behavioural or physiological arousal can be used to support the subjective rating. Heart rate [1], digital blood flow [2-4], simple measures of skin conductance [5] and plasma [1, 4, 6] and cerebrospinal fluid [1] catecholamine concentrations have been used in the assessment of preoperative anxiety and the effects of premedication.

Skin conductance reflects eccrine sweat gland activity and associated changes in the epidermis, and hence activity in the sympathetic sudomotor fibres [7]. Measurement of skin conductance has been used extensively in the psychophysiological investigation of anxiety and, more recently, the effects of anxiolytic and other psychotropic agents. The effect of morphine on skin conductance has not previously been studied.

The skin conductance waveform can be described by the baseline skin conductance level (SCL) and by the frequency of superimposed peaks (non-specific responses (NSR)) [7]. Both are increased in anxiety states [8, 9]. Presentation of an external stimulus evokes a skin conductance response (SCR), which is superimposed on the SCL and NSR. If a series of identical stimuli is presented, there is a progressive decrease in SCR amplitude until no response occurs (habituation). Subsequent presentation of a novel stimulus usually results in a large amplitude SCR (dishabituation) [10]. Habituation is slower, and dishabituation more reliably elicited, in anxious subjects [9]. Conversely, rapid habituation and a low incidence of dishabituation indicates that the subject has adapted readily to his environment. The change in SCL during presentation of a series of stimuli also reflects emotional arousal and adaptation [9].

It may be predicted that effective anxiolytic medication would reduce SCL and NSR, and that the change in SCL with time and rate of habituation would indicate superior adaptation to the environment compared with the unmedicated subject.

The first objective of this study was to investigate the differences in absolute values and patterns of change in skin conductance between unpremedicated patients, patients premedicated with diazepam and those premedicated with morphine under innocuous and stressful conditions. A second objective was to examine the relationship between these measures and subjective ratings of anxiety and sedation.

PATIENTS AND METHODS
The study was approved by the Hospital Ethics Committee. Informed consent was obtained from 45 patients undergoing elective orthopaedic or general surgical procedures under general anaesthesia. Exclusion criteria were pregnancy, age greater than 65 yr, neurological disease, diseases with potential neurological complications (e.g. diabetes), operations for malignancy, psychiatric illness, treatment with drugs with a sedative or anticholinergic action, and treatment with beta-blockers. Patients were excluded if they failed a simple clinical hearing test.
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On the morning of surgery, the patient's anxiety and degree of sedation were assessed using 10-cm visual analogue scales (VAS). The extremes of the anxiety VAS were designated "completely calm" and "the most worried I can ever imagine being"; those of the sedation VAS were "wide awake" and "so drowsy I cannot keep my eyes open". Patients were then allocated randomly to one of three groups. Approximately 90 min before surgery group D received diazepam 10 mg orally and group M received morphine 10 mg intramuscularly. Group ND (no drug) received no premedication on the ward, but had been informed at the time of recruitment that they would receive i.v. sedation with midazolam after completion of the study and approximately 40 min before anaesthesia and surgery.

Patients in groups D and M were studied 60–70 min after premedication, and those in group ND 40–50 min in advance of the time at which they would normally have been brought to theatre. On arrival in the theatre suite, patients rated anxiety and sedation as before, under the supervision of a nurse who was unaware of their study group.

Recording took place in a quiet, artificially-illuminated room adjacent to the theatre suite. Ambient temperature was 21–24 °C. Skin conductance was measured using an SC4 skin conductance coupler (Contact Precision Instruments) interfaced with an Amstrad PC1512 microcomputer. The sampling frequency was 10 Hz. The absolute accuracy of the SC4 coupler is 0.3 microsiemens (µS) and the maximum resolution is 0.003 µS. The minimum response criterion used in this work was 0.03 µS.

Two silver–silver chloride cup electrodes, each with a contact area of 0.8 cm², were attached to the palmar surfaces of the middle phalanges of the second and third digits of the patient’s non-dominant hand. The non-abrasive electrolyte paste, which was prepared by the hospital pharmacy, contained sodium chloride 0.05 mol litre⁻¹ [11]. Ten minutes was allowed for the electrodes to settle; patients rested quietly during this time.

Computer software had been developed (by S.M.G.) using Microsoft QuickBASIC v4.5 to provide an on-line display of the skin conductance waveform and to record the digitized data on disk. Computer-generated tones had been recorded using the Audiocard 300E (Speech Design). During recording of skin conductance, these tone files were called by the controlling program and replayed by the audiocard; thus recording of skin conductance data was not interrupted during the period of greatest interest immediately after stimulus presentation.

Skin conductance responses

Auditory stimuli recording (ASR). Patients lay supine with the eyes open and were informed that they would hear a series of "beeps". They were assured that there was no associated task requirement. Skin conductance was recorded for an initial period of 3 min when no stimuli were presented, during presentation of the auditory stimuli via occlusive headphones over 3 min and finally for 3 min with no stimuli. The stimuli comprised 11 tone pairs presented at 80 dB. Each tone lasted 0.8 s and the interval between the tones was 0.1 s. Tone pairs 1 to 10 were identical (1024 Hz and 634 Hz). The 11th pair consisted of the familiar first tone followed by a novel tone (1024 Hz and 380 Hz). In order that the patient could not anticipate stimulus presentation, the interstimulus intervals varied (10, 15 or 25 s); however, the presentation sequence was identical for each subject.

Anticipatory response before venepuncture. The patient was informed that an i.v. cannula was to be inserted. Immediately after this, skin conductance was recorded for 60 s, ending just before venepuncture.

Data analysis

The digital recordings of skin conductance were analysed using computer software, written (by S.M.G.) using Microsoft QuickBASIC v4.5, which allowed replay of the digitized data and display of the skin conductance waveform with automatic measurement and display of values of SCL and response amplitude. Differentiation between evoked SCR and NSR was by on-screen display of a "latency window" from 1 to 4 s after stimulus presentation.

An observer who was unaware of the patient allocation recorded the following measurements. The number of NSR greater than 0.03 µS in each of the recordings for each subject; SCL at the start of the ASR, immediately before presentation of stimuli 1, 2, 6 and 10, and the final value; SCL immediately before and 60 s after warning of venepuncture; the number of auditory stimuli which elicited an SCR greater than 0.03 µS before two consecutive stimuli failed to evoke an adequate response (the criterion for habituation used in this paper [12]); the occurrence of an SCR following presentation of the novel (11th) stimulus (dishabituation). If the patient had responded to the 10th stimulus, he was considered to have dishabituated only if the response to the 11th stimulus was greater than the preceding one.

Analysis of the serial measurements of SCL was carried out in accordance with the guidelines of Matthews and colleagues [13]. The area under the curve (AUC) of the graph of SCL vs time was calculated for each subject during the ASR, using the values of skin conductance measured at the six points described above, and during the 60 s before venepuncture, using the initial and final values of conductance. These values were used as summary measures of skin conductance and were considered further.

Differences between the groups for VAS, NSR and AUC were identified using the Kruskall–Wallis test. These were examined further using the Mann–Whitney test. Rate of habituation and the incidence of dishabituation in response to the novel stimulus were examined using the chi-square test. The Bonferroni correction was applied to offset the increased risk of type I error inherent in multiple comparisons, hence $P < 0.017$ was considered significant (i.e. 0.05/number of comparisons). Within-group changes in SCL and NSR were
analysed using the Wilcoxon matched-pairs rank sum test. Relationships between variables were examined using the Spearman rank correlation coefficient. In these cases $P < 0.05$ was considered significant. All values of $P$ are two-tailed. Minitab (Release 6.1.1), run on an Amstrad PC1512 microcomputer, was used for data analysis.

RESULTS

The groups were similar in sex ratio, age, height and weight (table I).

Skin conductance during ASR

The number of NSR in the ASR was similar in groups M (median 25, inter-quartile range (IQR) 9–39) and ND (median 26, IQR 14–45). The number occurring in group D (median 4, IQR 3–13) was significantly smaller than in group M ($P = 0.012$) and in group ND ($P = 0.0008$, Mann–Whitney test).

In groups M and ND, mean SCL increased after the first stimulus and remained greater than the initial value throughout the recording, but the changes from initial to final value were not significant. In group D, SCL decreased progressively during the ASR and the change was significant (median change $-1.18 \mu S$, $P = 0.005$, Wilcoxon matched-pairs rank sum test).

The median value of the AUC of the graph of SCL vs time in group D was $30.77 \mu S \cdot min$ (IQR 20.71–54.47). This was significantly smaller than the values in group M (median 61.61, IQR 36.70–72.53, $P = 0.009$) and group ND (median 60.93, IQR 54.60–102.80, $P = 0.0004$, Mann–Whitney test).

Habituation and dishabituation of the SCR

The patients were arbitrarily defined as low (0–3), medium (4–6) or high (7–10) responders on the basis of the number of the last stimulus which elicited an SCR before two consecutive “no-responses” (habituation). Dishabituation was defined as above.

There were no differences between the groups in both respects (chi-square test) (table II).

Anticipatory response

The number of NSR in the 60 s after warning of venepuncture (table III) was significantly smaller in group D than in group ND ($P = 0.005$, Mann–Whitney test). In all groups, the number of NSR occurring in this period was significantly greater than that recorded during the last 60 s of the ASR ($P = 0.001$ in all groups, Wilcoxon matched-pairs rank sum test).

There were no significant differences between groups in AUC during the 60 s in anticipation of venepuncture (Mann–Whitney test) (table IV). These values of AUC were compared with the values for AUC in the final 60 s of the ASR: there was a significant ($P < 0.002$) increase in all groups (Wilcoxon matched-pairs rank sum test).

Anxiety scores

Initial anxiety and sedation scores were similar in all groups (table V). The increase in anxiety score in group ND was significant ($P = 0.025$, Wilcoxon matched-pairs rank sum test) and the final score in this group was significantly greater than that in group D ($P = 0.013$, Mann–Whitney test).

There were significant increases in sedation scores in groups D ($P = 0.020$) and M ($P = 0.014$, Wilcoxon matched-pairs rank sum test), but there were no significant differences between the groups in respect of final sedation score.

Correlation between skin conductance and subjective variables

Spearman rank correlation coefficients, describing the relationships between the final ratings of anxiety and sedation and various measures of skin conductance recorded during the ASR described above, plus the initial value of SCL, were calculated for individual groups.

In group D, there was a significant correlation between the decrease in SCL during the ASR and the anxiety score ($r_s = 0.56$, $P = 0.035$). In group ND there were significant correlations between the anxiety score and the number of NSR ($r_s = 0.60$, $P = 0.006$).
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Table V. VAS scores (median (interquartile range)) for anxiety and sedation before premedication (initial) and on arrival in the theatre suite (final)

<table>
<thead>
<tr>
<th></th>
<th>Anxiety (mm)</th>
<th>Sedation (mm)</th>
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<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Group D</td>
<td>19 (7-46)</td>
<td>25 (20-31)</td>
</tr>
<tr>
<td>Group M</td>
<td>15 (6-32)</td>
<td>23 (10-37)</td>
</tr>
<tr>
<td>Group ND</td>
<td>26 (10-36)</td>
<td>35 (30-53)</td>
</tr>
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</table>

P = 0.019) and the change in SCL during the ASR (r_s = 0.55, P = 0.033). In the same group there was a significant negative correlation between the change in SCL and the final sedation score (r_s = -0.58, P = 0.022).

DISCUSSION

In general, skin conductance was less and showed a pattern indicating superior adaptation to the environment during the ASR in patients who received diazepam compared with those receiving morphine or no premedication. Similar effects of diazepam on skin conductance have been demonstrated in patients with anxiety disorder [14] and in stressed volunteers [15].

Although there appeared to be some depression of skin conductance by morphine, none of the indices was significantly different from those recorded from the patients who had received no premedication. In addition to their specific central nervous system effects, opioids produce a generalized decrease in arousal by their action on the central noradrenergic activating systems arising in the nucleus coeruleus in the midbrain. However, morphine had little effect on skin conductance, suggesting that skin conductance is not a non-specific index of sedation or anxiolysis, but may be more sensitive to certain groups of drugs, for instance those which act by facilitating GABA-ergic transmission. This idea is supported by the finding that cyclobarbitone causes a profound depression of skin conductance [16]; barbiturates facilitate GABA-ergic transmission via an action at specific receptor sites within the GABA receptor complex [17, 18].

Rate of habituation and the occurrence of dis-habituation appeared less sensitive to the effect of diazepam than the other measures, but this may reflect insensitivity of our test. In a pilot study in surgical patients, habituation had occurred in all subjects by the seventh stimulus. However, several patients in groups M and ND had not habituated after 10 stimuli, resulting in a ceiling effect. A larger number of stimuli might have allowed greater differentiation between the groups.

Benzodiazepines suppress other measures of sympathetic nervous system activity in patients awaiting surgery. Cerebrospinal fluid catecholamine concentrations were smaller in patients receiving diazepam than in unmedicated patients and those receiving placebo [1], and plasma adrenaline concentrations were reduced after administration of chloro-methyl-diazepam [4]. However, an increase in plasma adrenaline concentration following premedication with diazepam has been reported [6]. It is interesting that these authors found no increase in plasma adrenaline in patients who received papaveretum and hyoscine.

Oral nitrazepam [2] and oral chloromethyldiazepam [4] produce cutaneous vasodilatation as measured by digital pulse-volume plethysmography. Conversely, vasoconstriction is present in patients premedicated with pethidine and promethazine and those receiving papaveretum and hyoscine [3]. Anxious subjects have a high vasoconstrictor and sudomotor tone, resulting in a “cold sweat”. Thus it appears that benzodiazepines reduce both components of this familiar symptom of anxiety, whilst opioids are less effective.

Physiological changes occurring in anticipation of a threatening stimulus are a useful measure of anxiety. Fell and his co-workers [6] found that plasma adrenaline and noradrenaline concentrations were within the normal range after venepuncture in volunteers and suggested that venous cannulation did not produce a measurable stress response. We recorded a large increase in both the number of NSR and the SCL before venepuncture in all groups, and the suppression of skin conductance by diazepam became less marked. Where a prolonged recording was made after venepuncture, the increase in skin conductance was sustained for at least 5 min. The occurrence of a detectable response in our patients may reflect the greater levels of anxiety present in patients compared with volunteers, or a difference in sensitivity between the two techniques.

In surgical patients, significant correlations have been demonstrated between increases in plasma adrenaline and anxiety [6], and between heart rate and anxiety [1, 19]. We found significant correlations between anxiety and number of NSR in group ND, the change in SCL during the ASR in groups D and ND, and a negative correlation between sedation and change in SCL in group ND. These correlation coefficients were of magnitude similar to those reported between anxiety and various measures of skin conductance in stressed volunteers [20] and anxious patients [9]. The absence of any significant relationship between the subjective measures and skin conductance in group M supports our earlier observations about the lack of a relationship between the perceived anxiolytic or sedative effects of morphine and skin conductance.

Lader has suggested that NSR frequency is the best index of emotional arousal [8]. We found this to be true in unpremedicated subjects, but found that the change in SCL over the duration of the recording was also related to anxiety scores. To our knowledge the use of the AUC of the graph of SCL vs time has not been used previously in the analysis of skin conductance data. It is interesting that this summary measure, representing total skin conductance activity, was not related to either of the subjective measures in any group.

It is recognized that anxiolysis and sedation are separate psychopharmacological effects. We asked our subjects to rate both anxiety and sedation, as we wished to investigate whether measurement of skin conductance could differentiate between the two. We found no evidence to support this idea.
In conclusion, this study has shown that administration of diazepam to surgical patients produces a pattern of skin conductance consistent with a lower level of autonomic arousal and greater adaptation to the environment than in unpremedicated subjects and those receiving morphine. We suggest that skin conductance might be more sensitive to drugs facilitating GABA-ergic transmission than to drugs producing anxiolysis or sedation primarily by other mechanisms. We consider that measurement of skin conductance may be useful in the evaluation of other anxiolytic and sedative drugs in anaesthesia.

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REFERENCES