Skin conductance responses in patients sedated with midazolam or propofol

S. M. Geddes, W. M. Gray and A. J. Asbury

Summary

We have measured the skin conductance response under resting conditions and to innocuous auditory stimuli in 45 patients receiving midazolam (group M), propofol (group P) or no sedative drug (group ND) before minor hand surgery under local anaesthesia. Administration of the sedative drugs was titrated to the end-point of slurring of speech and ptosis. The mean dose of midazolam was 0.06 (SD 0.01) mg kg\(^{-1}\) and the mean infusion rate of propofol was 2.2 (0.39) mg kg\(^{-1}\) h\(^{-1}\). Subjective ratings of anxiety and sedation were measured using visual analogue scales. These were similar in groups M and P and significantly different from those reported by group ND (\(P = 0.001-0.005\)). However, measures of skin conductance in group M were significantly lower than in group P (\(P = 0.002-0.013\)) and group ND (\(P = 0.004-0.016\)). These measures were similar in groups P and ND. Skin conductance measures were related significantly to anxiety scores only in groups M and ND (\(P < 0.05\)). We conclude that skin conductance is not a non-specific index of sedative-anxiolytic action and therefore is not useful in comparative studies of anxiolytic drugs that exert their effects by different pharmacological mechanisms. (Br. J. Anaesth. 1994; 73: 345-349)

Key words


Skin conductance has been used extensively as a measure of sympathetic nervous system (SNS) activity in the psychophysiological investigation of anxiety. Skin conductance reflects eccrine sweat gland activity and associated changes in the epidermis, and therefore reflects activity in the sympathetic sudomotor fibres [1]. The skin conductance waveform consists of a baseline skin conductance level (SCL) with superimposed peaks (non-specific responses, NSR) which reflect bursts of sweat secretion and hence the frequency of impulses in the sudomotor fibres. SCL reflects the degree of filling of the sweat ducts and the hydration of the epidermis, which result from glandular activity [2]. Both NSR and SCL are raised in anxiety states [3, 4]. 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) [5]. Habituation is slower, and dishabituation more reliably elicited, in anxious subjects [4].

Skin conductance has been used also in the evaluation of anxiolytic drugs. We measured skin conductance in patients awaiting surgery under general anaesthesia and found significant differences between skin conductance recorded from patients premedicated with diazepam and those who received morphine [6]. However, these groups reported similar levels of anxiety and we suggested that it may be incorrect to assume that changes in skin conductance reflect anxiolytic activity. These changes may simply reflect different sensitivities which are not related to anxiolysis of the central neural component of skin conductance.

The main objective of this study was to investigate further the differences in sensitivity of skin conductance to sedative and anxiolytic drugs used in anaesthesia and to determine the value of skin conductance in the assessment of these drugs. A second objective was to examine the relationship between skin conductance 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 minor hand surgery under local anaesthesia. Exclusion criteria were pregnancy, age more than 65 years, neurological disease, diseases with potential peripheral neurological complications (e.g. diabetes, rheumatoid disease), psychiatric illness, current treatment with drugs with a sedative or anticholinergic action or treatment with beta-adrenergic blocking drugs. Patients were excluded if they failed a simple clinical hearing test. No patient had previous experience of surgery under local anaesthesia.

Patients did not receive sedative premedication on...
the ward. On arrival in the theatre suite, the patient's anxiety and degree of sedation were assessed using 10-cm visual analogue scales (VAS) under the supervision of the anaesthetist (S.M.G.). The two extremes of the anxiety VAS were designated "completely calm" and "the most worried I can ever imagine being"; and those of the sedation VAS, "wide awake" and "so drowsy I can't keep my eyes open".

Subjects were then allocated randomly to one of three groups (group M, midazolam, group P, propofol or group ND, no drug). An i.v. cannula was inserted and a suitable local anaesthetic block was performed in a standard fashion with appropriate monitoring. All blocks were performed by the same anaesthetist (S.M.G.).

Patients were transferred to a quiet artificially-lit room. Ambient temperature was between 21 and 24 °C. Two silver-silver chloride cup electrodes were attached to the palmar surfaces of the middle phalanges of the second and third digits of the hand that was not to be operated on. The electrolyte paste contained sodium chloride 0.05 mol litre−1 [7]. Five minutes were allowed for the electrodes to stabilize. Patients rested quietly during this time.

Skin conductance was measured and recorded using an SC4 skin conductance coupler (Contact Precision Instruments) interfaced with an Amstrad PC1512 microcomputer. Technical details of the skin conductance coupler and the recording software have been described previously [6].

BASELINE RECORDING

All patients wore occlusional headphones and skin conductance was recorded for 3 min while they lay with their eyes open. The patients were then asked to relax and talk quietly with the observer. The observer had been instructed to make the nature of the conversation neutral or reassuring. Patients were reminded that they might receive a sedative drug or no drug and were assured that further anxiolytic-sedative drugs would be available after completion of the recording and before transfer to the operating theatre.

Patients in group M then received an i.v. bolus of midazolam 0.02 mg kg−1 (to the nearest 0.1 mg) followed by further 0.01-mg kg−1 boluses at 3-min intervals until the observer detected slurring of speech and ptosis. Three minutes later the end-point was checked and additional midazolam given if necessary. No additional sedation was given during the second skin conductance recording. Patients in group P received an i.v. bolus of propofol 0.5 mg kg−1 (to the nearest 5 mg) over 30 s followed immediately by an infusion at a rate of 1 mg kg−1 h−1. The infusion rate was increased by 0.5 mg kg−1 h−1 every 3 min until the same end-point was reached. The infusion was continued at this rate for another 3 min, when the end-point was checked and the infusion rate adjusted if necessary. The infusion was continued at this rate throughout the second recording.

Drugs were given via a 200-cm length of fine-bore tubing and this tubing, the syringe, the anaesthetist giving the drug and the recording equipment were concealed behind a screen from the patient and observer both before and during administration. Thus neither the observer nor the patient knew which drug was administered or when a bolus was given or the infusion rate was changed. Patients in group ND received no sedative drug; a syringe was attached and the screen erected as for groups M and P. The observer talked quietly with these patients for approximately 10 min. The observer was unaware that the patient was receiving no drug until the administrator informed the patient that skin conductance recording was about to begin. The patient may have realized that no sedative had been administered, but he had been informed of this possibility.

Patients in all groups then rated anxiety and sedation as before, under the supervision of the observer.

SKIN CONDUCTANCE RESPONSES TO INNOCUOUS AUDITORY STIMULI (AUDITORY STIMULI RECORDING)

Patients were reminded of the nature of the stimulus sequence (see below) and the absence of task-requirement. They were asked to keep their eyes open during the recording. Skin conductance was recorded for an initial period of 3 min, during presentation of the auditory stimuli (tones) via headphones for 3 min and finally for 3 min with no stimuli. The stimuli were 11 tone pairs presented at 70 dBA [6]. Each tone lasted 0.8 s and the interval between the tones was 0.1 s. Tone pairs 1–10 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). So that the patient could not anticipate stimulus presentation, the inter-stimulus intervals varied and were either 10, 15 or 25 s. However, the presentation sequence was identical for each patient.

At the conclusion of the study, additional sedation was offered to all patients before transfer to theatre.

ANALYSIS OF SKIN CONDUCTANCE RECORDINGS

The digital recordings of skin conductance were analysed using the computer software which we have described previously [6].

An observer who was unaware of 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 and end of the baseline recording; SCL at the start of the auditory stimuli recording, immediately before presentation of stimuli 1, 2, 6 and 10, and the final value; the number of auditory stimuli which elicited an SCR of greater than 0.03 μS before two consecutive stimuli failed to evoke an adequate response (the criterion for habituation used in this paper [8]); and the occurrence of an SCR after presentation of the novel (11th) stimulus (dishabituation). Where the patient had not habituated (i.e. had responded to stimulus 8), the number of stimuli before habituation was taken as 10. Where the patient had responded to the 10th stimulus, he was considered to have dishabituated only if the response to the 11th stimulus was larger than the preceding one.
Skin conductance responses in sedated patients

Analysis of the serial measurements of SCL was carried out in accordance with the guidelines of Matthews and co-authors [9]. The area under the curve (AUC) for SCL vs time was calculated for each subject during the baseline recording using the initial and final values of skin conductance and during the auditory stimuli recording using the values of skin conductance at the six points described above. The values were used as summary measures of skin conductance activity and were considered further.

Differences between the groups for VAS, NSR and AUC were identified using the Kruskal–Wallis test and were further examined using the Mann–Whitney test. Rate of habituation and incidence of dishabituation were examined using the chi-square test. Bonferroni correction was applied to offset the increased risk of type 1 error inherent in multiple comparisons, hence \( P < 0.017 \) was considered significant (i.e. 0.05 per 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) was used for data analysis.

Results

The groups were similar in sex ratio, age, height and weight (table 1). In 27 of 45 patients, the surgical procedure was release of Dupuytren’s contracture.

Table 1 Patient characteristics (mean (range or sd))

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex (M:F)</th>
<th>Age (yr)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group M (n = 15)</td>
<td>12:3</td>
<td>51 (21-62)</td>
<td>1.74 (0.06)</td>
<td>69.6 (10.8)</td>
</tr>
<tr>
<td>Group P (n = 15)</td>
<td>10:5</td>
<td>48 (24-64)</td>
<td>1.71 (0.08)</td>
<td>67.4 (7.18)</td>
</tr>
<tr>
<td>Group ND (n = 15)</td>
<td>11:4</td>
<td>38 (15-65)</td>
<td>1.69 (0.14)</td>
<td>73.5 (13.2)</td>
</tr>
</tbody>
</table>

The higher incidence of this condition in males is reflected in the sex ratio in all groups. Thirty-five patients had brachial plexus blocks (group P, 10; group M, 13; group ND, 12) and the remainder had a combination of peripheral nerve or “carpal tunnel” blocks, or both.

The mean dose of midazolam was 0.06 (sd 0.01) mg kg\(^{-1}\). The mean maintenance rate of infusion of propofol was 2.2 (0.39) mg kg\(^{-1}\) h\(^{-1}\).

The number of NSR in the baseline recording was similar in all groups (table 2). There were no differences between the number of NSR in the baseline recording (3 min) and that occurring in the first 3 min of the auditory stimuli recording (pre-stimulus) in groups P and ND. In group M there was a significant decrease in the number of NSR from the baseline recording (\( P = 0.004 \), Wilcoxon matched-pairs rank sum test). The total number of NSR during the auditory stimuli recording in group M was significantly lower than in groups P (\( P = 0.002 \)) and ND (\( P = 0.011 \), Mann–Whitney test).

There were no differences between the groups in the AUC for SCL vs time during the baseline recording (Mann–Whitney test) (table 3). The value of AUC in the first 3 min of the auditory stimuli recording (pre-stimulus) was compared with that in the baseline recording for each group and was significantly greater in groups P (\( P = 0.001 \)) and ND (\( P = 0.001 \), Wilcoxon matched-pairs rank sum test). The median value of AUC for the entire auditory stimuli recording was significantly lower in group M than in groups P (\( P = 0.013 \)) and ND (\( P = 0.016 \), Mann–Whitney test). In group M only there was a significant difference between the initial and final values of SCL in the auditory stimuli recording (median change \( -1.19 \mu S \); \( P = 0.001 \), Wilcoxon matched-pairs rank sum test).

HABITUATION AND DISHABITUATION

The number of SCR before habituation was significantly lower in group M (median 2, interquartile range (IQR) 0–5) than in group P (median 7, IQR 3–10; \( P = 0.005 \)) and ND (median 10, IQR 1–10) (\( P = 0.004 \), Mann–Whitney test). The novel stimulus (pair 11) elicited dishabituation in four

Table 2 Number of non-specific responses (NSR) during the baseline recording (3 min), during the first 3 min of the auditory stimuli recording (pre-stimulus) and the entire auditory stimuli recording (ASR) (median (interquartile range)). \( *P < 0.017 \) compared with group M; \( \dagger P < 0.05 \) pre-stimulus period compared with baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Pre-stimulus</th>
<th>Total in ASR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group M (n = 15)</td>
<td>11 (5–18)</td>
<td>3 (1–7)†</td>
<td>9 (2–15)</td>
</tr>
<tr>
<td>Group P (n = 15)</td>
<td>10 (4–17)</td>
<td>13 (9–17)*</td>
<td>27 (15–38)*</td>
</tr>
<tr>
<td>Group ND (n = 15)</td>
<td>9 (3–17)</td>
<td>9 (3–22)</td>
<td>29 (8–70)*</td>
</tr>
</tbody>
</table>

Table 3 Area under the curve (AUC) for skin conductance level (SCL) vs time during the baseline recording (3 min), the first 3 min of the auditory stimuli recording (pre-stimulus) and the entire auditory stimuli recording (ASR) (median (interquartile range)). \( *P < 0.017 \) compared with group M; \( \dagger P < 0.05 \) pre-stimulus period compared with baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Pre-stimulus</th>
<th>ASR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group P</td>
<td>36.75 (20.85–39.00)*</td>
<td>16.70 (9.50–113.50)*</td>
<td>46.77 (24.44–62.62)</td>
</tr>
<tr>
<td>Group ND</td>
<td>36.75 (20.85–39.00)*</td>
<td>16.70 (9.50–113.50)*</td>
<td>46.77 (24.44–62.62)</td>
</tr>
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</table>
patients in group M. This was a significantly smaller number than in groups P (13; P < 0.001) and ND (11; P < 0.02, chi-square test).

ANXIETY AND SEDATION

Initial anxiety and sedation scores were similar in all groups (table 4). After administration of the sedative drug, anxiety scores decreased significantly in groups P (P = 0.031) and M (P = 0.007, Wilcoxon matched-pairs rank sum test) and the final scores were significantly lower in these groups than in group ND (P = 0.005, P < 0.001, respectively; Mann–Whitney test).

There were significant increases in sedation scores in all groups (group M, P = 0.001; group P, P = 0.001; group ND, P = 0.03; Wilcoxon matched-pairs rank sum test). Final sedation scores were significantly higher in both groups P and M than in group ND (P < 0.001 in both cases, Mann–Whitney test).

CORRELATION BETWEEN INDICES OF SKIN CONDUCTANCE AND SUBJECTIVE VARIABLES

Spearman rank correlation coefficients (r_s) describing the relationships between the final ratings of anxiety and sedation and the various measures of skin conductance during the auditory stimuli recording were calculated for the individual groups. In group M there was a significant correlation between anxiety score and AUC during the auditory stimuli recording (r_s = 0.57, P < 0.05) and the value of SCL at the beginning of the auditory stimuli recording (r_s = 0.52, P < 0.05). In group ND there was a significant correlation between the number of NSR and anxiety score (r_s = 0.54, P < 0.05).

Discussion

In summary, the findings of this study were that patients sedated with midazolam, titrated to the end-point of ptosis and slurring of speech, had lower skin conductance activity and showed a pattern of change of skin conductance which indicated superior adaptation to the environment compared with patients sedated to the same end-point with propofol. The suppression of skin conductance by midazolam was not overcome by the arousing effect of a series of innocuous auditory stimuli. Skin conductance recorded from the patients who received propofol was similar to that recorded from patients who had received no sedation.

It might be assumed that, as sympathtic nervous system (SNS) activity reflects emotional arousal, suppression of this activity (in a group of patients who had reported feelings of anxiety) would indicate anxiolysis. Thus we might conclude that the patients who received midazolam were significantly less anxious–more sedated than those who received propofol. However, this was not supported by clinical observation or VAS scores.

Measurement of anxiety poses many difficult problems. There is inconsistent agreement between self-report and other techniques such as behavioural and performance tests and measurement of SNS activity. Although self-report must be the "gold standard", subjective assessment of a complex emotion, such as anxiety, is difficult, and particular reservations have been expressed about the validity of this technique in assessing anxiety in patients before operation [10, 11].

These problems become more complex when we attempt to measure the anxiolytic effect of a drug [12]. Despite this, measures of SNS activity are commonly used as indices of anxiety and anxiolytic effect. In human volunteers and patients with anxiety disorder, skin conductance has been used in studies comparing the anxiolytic effect of standard clinical doses of benzodiazepines and beta-adrenergic blocking drugs [13, 14], barbiturates [15], halo-peridol and chlorpromazine [16], and amitriptyline [17]. Although the designs of these studies were very different, skin conductance was reliably suppressed by the benzodiazepines and this was generally interpreted as reflecting superior anxiolytic effect.

In patients awaiting surgery under general anaesthesia, we found that skin conductance activity was lower and that the pattern of change indicated superior adaptation to the environment in patients premedicated with diazepam than with those who received morphine [6]. However, subjective ratings of anxiety and sedation were similar in both groups and we suggested that skin conductance might not be a valid measure of the anxiolytic action for all drugs, but that differences in skin conductance might reflect differences in sensitivity of the central neural component of skin conductance to the drugs used and that these effects might not necessarily be related to the anxiolytic effect.

The results of the current study support this idea. Groups M and P reported similar degrees of central nervous system depression, but only with midazolam was this reflected in changes in skin conductance; although anxiety and sedation scores were similar in groups M and P and were significantly different from those reported by group ND, there were no differences between skin conductance measures recorded in groups P and ND.

It should be noted that the end-point for drug administration in our patients was based on the degree of sedation rather than anxiolysis because sedative effect is judged more easily by an observer, and observer and subjective assessments for sedation are in greater agreement than for anxiolysis [18]. However, it is recognized that anxiolysis and sedation are distinct psychopharmacological effects [19] and so there remains the possibility that skin

<table>
<thead>
<tr>
<th>Table 4</th>
<th>VAS scores (median (interquartile range)) for anxiety and sedation scores before (initial) and after (final) administration of the sedative drugs. * P &lt; 0.05 compared with initial value, †P &lt; 0.017 compared with group ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (mm)</td>
<td>Sedation (mm)</td>
</tr>
<tr>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Group M 25 (8–36)</td>
<td>10 (7–20)*†</td>
</tr>
<tr>
<td>Group P 34 (19–48)</td>
<td>19 (13–29)*†</td>
</tr>
<tr>
<td>Group ND 27 (22–55)</td>
<td>30 (22–57)</td>
</tr>
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British Journal of Anaesthesia
Skin conductance responses in sedated patients

conductance reflects the "pure" anxiolytic effect which is a property of the benzodiazepines, but not the less specific sedative actions of agents such as propofol. This question cannot be answered on the basis of current knowledge.

The correlation coefficients provided only weak support for the idea of a relationship between suppression of skin conductance and the anxiolytic effect of the benzodiazepines. In the unmedicated group, there was even less support for a relationship between anxiety and skin conductance. It follows that no conclusion can be drawn from the absence of a relationship between the subjective variables and skin conductance in group P.

In conclusion, skin conductance may be of value in the assessment of anxiety, but its place in the evaluation of the efficacy of anxiolytic and sedative drugs used in anaesthesia is less clear. Our results suggest that skin conductance cannot be used as a non-specific index of sedative-anxiolytic effect and therefore is not suitable for comparative studies of drugs exerting their effects by different pharmacological mechanisms. Similar limitations may apply to other measures of SNS activity currently used in the assessment of anxiolytic drugs. However, measurement of skin conductance may be useful when comparing drugs with a similar mode of action, for example benzodiazepines. The place of skin conductance in the measurement of anxiolytic effect cannot be assessed fully until we have more information about the central neural pathway of skin conductance and the major neurotransmitter systems involved in the production of anxiolysis.

Acknowledgements

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References