THE QUANTITATIVE ASSESSMENT OF PREMEDICATION

BY

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It is now widely accepted that one of the principal functions of premedication is the relief of anxiety in the pre-operative period. This being so, the main problem in quantifying the effects of premedication is the measurement of pre-operative anxiety or the extent to which this has been allayed by premedicant drugs. The measurement of anxiety is a subject which concerns not only the anaesthetist but also the psychiatrist, the pharmacologist and the psychophysiologist. There are, therefore, many established methods of measuring and quantifying anxiety documented in the literature of each of these specialties and it is the purpose of this paper to consider their applications and limitations, particularly in the clinical evaluation of premedicant drugs.

Before embarking on a discussion of the methods of measuring anxiety it is worth defining the term "sedation" which is frequently used in studies of anxiety. In a previous paper (Norris and Nisbet, 1963) it was pointed out that the word "sedation" is derived from the Latin verb sedare to settle; a sedative is a drug which tends to soothe (Concise Oxford Dictionary). It is considered, therefore, that in the present context sedation is a state in which pre-existing anxiety is relieved or lessened, or in which signs of anxiety do not develop in circumstances in which they would normally be expected to do so. Sedation is not, however, synonymous with drowsiness.

MEASUREMENT OF ANXIETY: THE SEDATION THRESHOLD

One approach to the measurement of drug effect on anxiety is that used by Shagass who, in 1956, described his "sedation threshold". Measured doses of amylobarbitone are slowly administered intravenously at regular intervals until speech is slurred and characteristic electroencephalographic changes are seen. The amount of drug required to produce this standard end point is measured and this is defined as the "sedation threshold". By comparing the amount of drug required to produce this end point in different groups of patients their level of anxiety may be compared, and by using different drugs in the same patients the relative potencies of the drugs may also be compared. This technique is of less value where narcotics with their undesirable side effects are being tested or where the modern "anxiolytic" drugs, which are claimed to relieve anxiety without clouding consciousness, are being tested. While this method gives much information of pharmacological importance in evaluating the comparative potency of sedative drugs, it is of limited value in the context of clinical studies of premedication where the drugs are normally administered by intramuscular or oral routes. It is usual in clinical practice, therefore, to administer a predetermined dose of drug and measure the end point produced.

THE SUBJECT'S IMPRESSIONS

Since anxiety is a state of mind experienced by the patient it would seem reasonable to base an assessment on the patient's own statement. Attempts to do so range from asking the patient to grade his anxiety as "severe", "mild" or "nonexistent" to more complex questionnaires such as used by Taylor (1953). In the immediate pre-operative period complex questionnaires are of limited value, but simple evaluation by the patient of the effect of his premedication has been used by Brandt, Lui and Briggs (1962) and Murray Bechtoldt and Berman (1968) and found to correlate well with an observer's impression of the degree of sedation obtained.

The completion by the patient of a questionnaire in the postoperative period evaluating his feelings after premedication has been used by Feldman (1963). Although just over 50 per cent of his questionnaires were returned, he found them of value in this study.

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The limitations of these methods are that patients differ in their assessment of their anxiety. This may be conditioned by their normal mode of life and their basal anxiety level. The answers may also be conditioned by what the patients feel is expected of them. Some will be reluctant to admit that they are anxious lest they are considered weaklings, whereas others, because of preconceived ideas or previous experience, may expect to be anxious at this time and profess to be so for this reason. The accuracy of the answers may be further affected by drugs which cloud consciousness or produce amnesia. At the best such impressions are difficult to quantify except in a very crude fashion. This technique is of more value in comparing one patient's state before and after drug therapy than in comparing the effect of the same drug on different patients.

**THE USE OF A TRAINED OBSERVER**

Most studies of anxiety and sedation are based on the use, in part at least, of a trained observer. Such an observer assesses the degree of anxiety present on the basis of certain clinical signs. Wright (1954) sets forth an anxiety check list of eighteen points which the observer should note and his assessment is based on the number of positive findings in this list. Such signs include the patient's appearance, the temperature of his skin, perspiration, the method of speech, the presence or absence of tremor, etc. Such a proforma may be used to 'grade anxiety by listing the number of points considered indicative of anxiety and expressing the number of positive findings as a percentage of the possible total. In most studies, however, the observer tends to form an impression of the patient, perhaps subconsciously using a check list, and grades him according to a fairly crude scale of mild to severe anxiety or mild to profound sedation. The value of the observer's impression increases with his experience and the regularity of his carrying out such assessments. It is maximal where sedation is profound or anxiety is acute, but as these two merge and the patient is awake, alert but apparently unworried, there is a greater possibility of error. Many of the so-called anxiolytic drugs now used in premedicant studies produce patients in this mid-zone and it is here that objective confirmation of the observer's opinion is particularly required.

Unreliable results may be obtained when an observer is inexperienced in this type of assessment or does not closely follow the same routine in each case. As the observer records his own subjective impression of the patient, widely varying results may be obtained when more than one observer is used even in the same study (Stetson and Jessup, 1962, 1963). In spite of these qualifications, the work from Belfast (Dundee, Moore and Nicholl, 1962; Morrison, Hill and Dundee, 1968) demonstrates the reproducibility of the findings of several observers working in close cooperation to predetermined criteria at regular intervals.

**OBJECTIVE SIGNS OF ANXIETY**

While anxiety and sedation are basically subjective responses, Beecher (1959) in his classic work has shown that such subjective states are usually associated with objective changes. Anxiety is accompanied by the exhibition of many physiological changes and modern psychophysiological methods are directed towards the measurement and recording of basal levels of such physiological variables or of changes in response to stimuli. Increase or decrease in autonomic function may be demonstrated by alterations in such variables as heart rate, blood pressure, electrical resistance or potential in skin, blood flow through skin and muscle, gastric motility, muscle tone, eye movements and the size of the pupil, and changes in the electrocardiogram and electroencephalogram. In addition, performance tests, reviewed by Steinberg (1959) and Goldberg (1959), such as measurement of reaction time and speed and accuracy of mental arithmetic have been used to demonstrate and quantify levels of anxiety. The principles and methodology of measuring many of these variables are dealt with in detail in the works edited by Venables and Martin (1967) and Brown (1967). Anxiety also leads to hyperventilation which is reflected in the lowering of the carbon dioxide levels both in blood and in the expired air. In addition, alterations in the plasma and urinary steroid levels occur in responses to psychological stress (Hamburg, 1962) and these can be measured and recorded.

It is clear, therefore, that there is no lack of objective evidence of anxiety and sedation which, given adequate time, facilities and ancillary per-
sonnel, a research worker may use in his studies. Many of the objective measurements which have been mentioned can be studied in regard to three factors: (1) the resting level, (2) the change in response to a specific stimulus, and (3) the variation around the mean level which takes place in a period of time. Such measurements are interrelated and this presents difficulties which will be discussed later.

LIMITATIONS IN CLINICAL APPLICATION

One of the limiting factors in the use of many of the methods described above is that the performance of the tests disturbs the state of sedation achieved by the previous administration of the drugs. Performance tests, or the insertion of needles to take blood or for electromyographic techniques, fall into this category. The use of the electroencephalograph, as described by Corssen and Domino (1964) is clearly of limited value in the anaesthetic room. The presence of much complicated apparatus may appear rather terrifying to the patient and this in some circumstances may limit the use of more complex techniques, but modern developments in the field of radiotelemetry should reduce this particular problem.

Ideally, information should be obtained and recorded continuously over a short period of time in such a way that the patient is not disturbed after the initial application of the sensing device. Additional information may be obtained by using equipment with which the patient is familiar such as the sphygmomanometer cuff and it has been shown (Norris and Telfer, 1968a, b) that total forearm blood flow may be measured with minimal disturbance to the patient.

RESTING LEVELS

Having selected suitable tests, procured sufficient apparatus and achieved such skill as to ensure that valid and reproducible results are obtained, further difficulties await the worker in this field. While there is a gradual change in the resting levels of many physiological variables from the deeply sedated state through wakefulness to acute anxiety, resting levels as such are difficult to obtain and measure. Thus, for example, using the measure which has proved so successful in quantifying anxiety in psychiatric practice—the recording of basal skin potential or resistance (Lader and Wing, 1966)—it has been shown by Shackel (1959) that to produce accurate results one must sandpaper or drill the skin at the site of the electrode application. This is a disturbing practice which is not acceptable in the study of premedication. True basal levels of many of the variables are also difficult to obtain in the short time which is available to the anaesthetist—a psychologist may take the lowest value obtained over many days.

RESPONSE TO STIMULI

Reliance is therefore placed more on the accepted method of recording change in these measures in response to stimuli. The pre-operative period is well supplied with naturally occurring stimuli—the transfer of the patient from ward to anaesthetic room and either the application of a face-piece or the preparation for and injection of an intravenous agent. Many of the physiological responses to these stimuli can be very easily recorded. The pattern of response to stimulus, however, is not invariably a smooth progression as it has been shown (Hendry, Norris and Nisbet, 1963; Nisbet, Norris and Brown, 1967) that paradoxical results may be obtained in the patient who is very drowsy and is awakened or in the patient who is acutely anxious. A similar pattern is found when measuring forearm blood flow (Telfer and Norris, unpublished observations). Such patients, however, the acutely anxious or the deeply sedated, are those who are most readily identified by the observer’s assessment and in the group who are awake but neither deeply sedated nor acutely anxious there is normally a progressive increase in autonomic activity which can be recorded by the objective tests suggested. It is in this middle group of patients that the objective tests are of particular value. Williams and Jones (1968) comment on the previously mentioned fact that a stressful stimulus may elicit different patterns of response in different patients. Thus, one individual may show an increase in muscle tone or change in electrical activity in the skin while another may show a marked rise in heart rate and another still a marked rise in blood pressure in response to the same stimulus (Malmo and Shagass, 1949; Lacey and Van Lehn, 1952).

Thus, the use of any single objective measure, while it is easy to quantify in units appropriate to the variable measured, cannot be guaranteed on its
own to give a valid measure of anxiety throughout the entire range of anxiety and sedation in any one individual, particularly in the clinical situation in which premedicant drugs are studied. It is usual, therefore, to combine measurement of a number of physiological variables either on their own or with the observer’s impression of the patient in the form of a scoring system.

SCORING SYSTEMS

By allocating points to the various desirable responses and subtracting points for undesirable qualities, scoring systems have been devised by Smith and Jeffries (1959) and Dundee, Moore and Nicholl (1962). In this way controlled clinical trials have been employed to evaluate the effect of different sedative drugs.

By considering subjective evaluation together with the results from several different objective tests, we may obtain a better overall assessment of the state of the patient. Such an approach is widely used in medicine and one may compare it to the normal diagnostic approach to a patient with a duodenal ulcer. In this case a history is taken, a clinical examination is undertaken and specific tests such as a fractional test meal, a barium meal and fiberoscopy may be performed. None of these by itself is infallible but when the results of all of them are put together the more positive findings there are in any one case the more likely is the diagnosis to be correct. The surgeon then has recourse to laparotomy and the percentage accuracy of each individual test may be assessed. No such final recourse is available in the measurement of anxiety but a similar principle may be applied.

The observer’s assessment alone may be used to construct a scoring system, awarding points on an arbitrary basis to the degree of anxiety noted by the observer. Similarly, the objective measures which have been described are easily quantifiable in the units appropriate to their measurement.

A scoring system combining the observer’s impression of the patient with simple measures of blood pressure and heart rate before and after stimulus has been described (Nisbet and Norris, 1963). The advantages of such a system are that in the areas where sedation is profound or anxiety manifest the observer’s impression can be given due weight and any inaccuracies in the objective measures at these extremes can be neutralized. Conversely, in the middle range where the patient is awake and anxiety or sedation is not easily distinguished by the observer the objective measures are at their most accurate and will significantly add to the accuracy of the assessment. Over a period of six years, fairly reproducible results have been obtained during repeated blind trials with a standard drug (morphine 10 mg) as shown in table I.

<table>
<thead>
<tr>
<th>Trial No.</th>
<th>Mean</th>
<th>“Good” sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.80</td>
<td>42%</td>
</tr>
<tr>
<td>2</td>
<td>6.10</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>6.04</td>
<td>42%</td>
</tr>
<tr>
<td>4</td>
<td>6.20</td>
<td>44%</td>
</tr>
<tr>
<td>5</td>
<td>5.60</td>
<td>36%</td>
</tr>
</tbody>
</table>

In compiling such a scoring system care must be taken to allocate points so that the maximum score is obtained by the patient who fulfils most or all of the criteria which the observer considers he requires from his premedicant drug. Our own scoring system gives a high score to the patient who is relaxed and drowsy and shows a fall in blood pressure and heart rate from the previously recorded ward level and who does not react to stimuli. Others, however, who might wish their patient awake and co-operative, although not showing signs of anxiety, might consider drowsiness to be undesirable and subtract marks from the total score. Thus, as Doughty (1959) has stated, one must have an ideal patient in mind when preparing a scoring system.

ANALYSIS OF RESULTS

The main object of quantifying subjective responses is to allow the results to be analyzed statistically. This problem is well discussed by Hill (1967). The so-called parametric analyses, such as the Student t test, may not properly be applied to figures arbitrarily allocated to such conditions as “good” sedation or “moderate” anxiety where the two are not mathematically related. Similarly, figures in a scoring system may be obtained which are equal, for example 7 out of 10, but represent positive and sometimes negative results from different tests. The use of scoring
systems is, however, based on the belief that if the tests are suitably chosen and scores allocated correctly the results should represent an overall picture of the patient's condition and therefore the previously quoted figure of 7 out of 10 will always represent a patient who shows 70 per cent of the selected signs of sedation (Norris and Nisbet, 1963).

While few scoring systems can be proved to produce a linear scale and thus non-parametric analyses may be required, Anderson (1961) concludes from a lengthy study that parametric analyses are often useful in such psychological studies. The decision as to what method of analysis is applicable should be taken after consultation with a statistician, preferably before the study commences. Lacey (1956), in reviewing the many conflicting results which have been published on the analysis of skin resistance and potential measurements using various complicated statistical techniques, attributes this in part to the fact that some of the mathematical assumptions are not justifiable on physiological grounds.

The use of objective measurements gives us results which are more suitable for statistical analysis but here also difficulties remain. For example, are we justified in assuming that a person whose heart rate rises by 40 on stimulation is twice as anxious as a patient whose heart rate rises by only 20?

Wilder (1962) draws attention to the "law of initial values" which briefly states that the lower the resting value of a physiological variable the greater the rise in response to stimulus. Many complex formulae have been used to relate response to initial value (Lacey, 1956; Stein-schneider and Lipton, 1965; Heath and Oken, 1965), and there is no generally agreed solution to this problem. If, however, each group studied contains patients whose resting values are similar, the problem is minimal. Alternatively, any variation from resting level beyond certain arbitrarily set limits may be counted as a "response" irrespective of its magnitude. Some form of compromise is normally reached and few accept the view of Blundell and associates (1959) that such results are not suitable for statistical analysis.

The analysis of results of similar trials is dealt with in detail in the works of Mosteller (1959) and Spicer (1959), to which the reader is referred.

**DISCUSSION**

Clearly, the methods of quantifying the effects of premedication still leave much to be desired. While subjective assessment by an observer has stood the test of time where the more potent sedative drugs are involved, the present trend is towards using drugs which relieve anxiety while producing little hypnotic effect. It is in this field that the observer falls short most often. Here Root (1962) has pointed out that judgements may be influenced by variables unrelated to the main effects of the drugs. While objective measures such as the psychogalvanic reflex and the measurement of skin resistance have been used in experimental studies by Carpenter and others (1962) and Stoneback, Rudman and Lumpkin (1964), when they are employed in patients in the anaesthetic room the results, although still of some value, are much less predictable. Objective psychological tests have a greater chance of success when it is possible to obtain a baseline over a period of hours or days and where the range of anxiety and sedation does not extend to deep sedation or severe anxiety.

It has been clear in our studies that when a patient reacts to a placebo and appears well sedated after either oral lactose or an injection of saline it is quite impossible to distinguish him from the truly sedated patient by any of the objective tests mentioned in the previous section.

Despite the difficulties in applying statistical tests to the measures of sedation involved in scoring systems of one or other type mentioned by Anderson (1961), the use of parametric and non-parametric statistics has found a place in this type of work when properly applied. The combined use of the observer's assessment plus simple painless objective methods in a scoring system appears to offer the best of both worlds as at present available. Instruments which allow continuous monitoring of a number of physiological variables without discomfort to the patient over a period of time increase the facility with which this can be done. As there is a wide and unpredictable response in different patients to the same stimulus, the more variables that are measured the more likely is the true state of affairs to be revealed.

So far only methods of measuring anxiety in the pre-operative period have been discussed. The effects which premedicant drugs may have on the
course of anaesthesia or on the postanaesthetic state have not been considered. It is felt that the limitations on the use of scoring systems and of statistical analysis applied thereto are increased even further when too many facets of a drug's action are measured at one analysis (Spicer, 1959; Lasagna, 1959). For this reason it is felt better to measure, by whatever means, the principal effect of the drug, in this case the relief of anxiety, and only then to balance the undesirable effects against these results (Campbell, Masson and Norris, 1965).

Whatever method of assessment is employed by an observer in measuring the sedative effects of a drug in relieving anxiety, it is essential that a well-designed clinical trial following the now well-recognized pattern (Dunne, 1967) should be employed. In particular, where a new method of assessment is in use a placebo should be included among the active remedies, if only because of the placebo effect of the observer's enthusiasm, particularly on repeated visits (Morrison, Hill and Dundee, 1968).

The advent of new drugs has brought many enthusiastic reports of their application in the field of premedication. Uncontrolled trials of such drugs, no matter how enthusiastic their presentation, may add little of practical value to our knowledge of the subject. It is to be hoped that the development of more accurate methods of measuring and quantifying anxiety and sedation will lead to a fuller appreciation of the effects of drugs both old and new in the field of premedication.

CONCLUSION

Many methods of measuring and quantifying the effects of premedication in the relief of anxiety exist. The subject's impression, the observer's impression, and the application to anaesthetic practice of objective measurements which have been used in psychopharmacological practice all have their advantages and limitations. The problems of analyzing statistically the results obtained by any combination of measures in a scoring system are considerable. From the evidence presented it is suggested that a combined method based on the observer's impression and the results from well-chosen objective measurements offer the best possible solution at the present time.

REFERENCES


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FIFTH INTERNATIONAL CONGRESS ON ANAESTHESIOLOGY

The Congress will take place in Kyoto, Japan, from October 2 to 8, 1972. The Belgian Professional Association of Specialists in Anaesthesia and Reanimation is to organize a three-weeks group tour from Brussels to the Far East, open to all anaesthetists of Western Europe and their families. The journey can thus be accomplished on the most advantageous terms. Booking is done on guaranteed periodical payments in advance.

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