OBJECTIVE MEASUREMENT OF SEDATION

I: INTRODUCTION: GENERAL CONSIDERATIONS

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SUMMARY

The primary function of premedication today is to allay anxiety. Thus the methods used clinically to assess premedicant drugs should be capable of measuring the degree of sedation produced. Subjective assessment alone is liable to error and difficult to quantify. Objective signs of anxiety and sleep have been described and used by others to measure these subjective responses. Some of this work is reviewed. The possible use of a scoring system based on objective signs is examined and the difficulties which result from the inclusion of many variables are indicated, and ways in which they may be minimized are discussed. Some problems of statistical analysis of data obtained in this way are discussed.

The changing pattern of premedication over the years has been reviewed by Shearer (1960). Many of the indications for which premedication was prescribed in the past do not now apply and most anaesthetists would agree with Feldman (1963) that the main function of premedication today is to allay anxiety in the immediate pre-operative period. Much of the recent work on premedicant drugs has been concerned as much with side effects as with sedation; for example, with post-operative vomiting (Riding, 1960) and antanalgesia (Dundee and Moore, 1960). The ideal drug will produce sedation without considerable side effects but we are perhaps in danger of finding drugs with useful side effects, such as anti-emetic activity, and mild sedative properties. The primary need is, therefore, to study sedation.

SEDATION

Sedation is a term applied loosely by many clinicians to include such states as euphoria, drowsiness, immobility, reduced basal metabolic rate and tranquillity. The word sedation is derived from the Latin sedare, to settle; a sedative is a drug which tends to soothe (Concise Oxford Dictionary). It may involve the patient in a subjective response which is positively pleasant or simply minimize an unpleasant experience.

Sedation is, therefore, not synonymous with drowsiness and where drowsiness and restlessness co-exist the patient cannot, by definition, be described as sedated. This distinction is not always clearly observed when attempts are made to measure sedation.

METHODS OF MEASUREMENT

Sedation is basically a subjective response, that is a sensation experienced by the patient. Beecher (1959) in his classic work has shown that such subjective states are usually associated with objective changes, that is changes which can be recorded by an observer and which in many cases can be quantified. Clinical methods of measuring sedation, therefore, fall into three main groups:

1. those based on the subject's impressions;
2. those based on the assessment of the patient by a trained observer;
3. those involving systematic measurement of objective signs.

The Subject's Impressions.

The subject's impressions recorded at the time of drug action are liable to certain errors. Stoical patients will not admit to anxiety while others will not resist the temptation to dramatize a situation in which they have, over a long period, been conditioned to expect anxiety. These errors may be magnified by the method of questioning, which may suggest that a certain answer is expected. If the subject's impressions are sought at

473
a later date, as by a questionnaire, further errors may be introduced. The patient may have forgotten his sensations after premedication, or his reaction may be clouded by memory of postoperative discomforts. Recollection may also be impaired by drug-induced amnesia.

Feldman (1963), in a careful study of the effects of premedication, received information from just over 50 per cent of the patients questioned. The reasons why the others did not reply are open to speculation. The patients may have lacked a strong social sense or possibly they did not want to stir up unpleasant memories. On the other hand, the numbers of those who did reply may be weighted in favour of patients who wished to record an unpleasant experience or an unexpectedly pleasant experience.

These errors aside, it is difficult for an untrained observer to assess the degree of anxiety from the patient's statements alone as these will reflect both his temperament and his way of life. Some of these criticisms will become less valid as the experience of the observer increases.

Assessment by an Experienced Observer.

This is sometimes referred to as a subjective assessment and in so far as it is based on the patient's statements this is true. Much of the information obtained by the observer is, however, based on the perhaps subconscious recognition of some of the objective signs of anxiety. The manner of speech, nervous movements of the arms and eyes, colour, vasoconstriction and sweating may be taken into account in making the assessment.

As different observers may give varying degrees of emphasis to either the subject's impressions or their own observations, it is important that in a comparative study the number of observers should be limited—ideally to one.

Unless the observer makes a conscious effort to record each of the signs of anxiety and uses a standard routine, his results will tend to vary from case to case. Furthermore, these signs are under the voluntary control of the patient and may be suppressed or exaggerated.

Once again this method does not lend itself to a quantitative assessment of sedation.

Measurement of Objective Signs.

The objective signs of sedation may be considered in two groups. Anxiety is the antithesis of sedation and in a stressful situation the absence of the signs of anxiety may be regarded as evidence of sedation. It is convenient to describe this absence of signs of anxiety as "negative" evidence of sedation. When a patient is sedated he is protected from stressful and other stimuli and proceeds towards a state of sensory deprivation. When this state is well advanced the patient will tend to sleep, because of the lack of arousal stimuli. The presence of the physical signs associated with sleep are, therefore, regarded as "positive" evidence of sedation.

Anxiety.

Of the observed signs of anxiety many can be measured in quantitative terms. Hypertension and tachycardia due to the autonomic response to stress are well known (Malmo and Shagass, 1949). Some of the symptoms of anxiety are due to increased muscle tension. Sainsbury and Gibson (1954) compared muscle tension in healthy and anxious subjects and found increased muscle tension in the latter group. This may be responsible for an increase in the reaction time.

Sainsbury (1955) also endeavoured to devise a means of recording gestures in a quantitative way and recorded heart rate concurrently as supporting evidence of emotional disturbance. Anxiety was found to be related to the number of gestures and accompanied by an increase in the heart rate.

The galvanic skin response to stress has also been studied by Malmo and Shagass (1950). The skin resistance falls during anxiety due to an increase in sweat gland activity.

Sleep.

It is likewise possible to measure certain aspects of the sleep process (Kleitman, 1939). There is a moderate fall in blood pressure and heart rate and a diminution in rate and depth of respiration, which characteristically becomes regular.

Brazier and Beecher (1952) studied the electroencephalographic changes and made quantitative measurements of the amount of alpha and delta activity in subjects, awake, asleep, and just before and after movements made in sleep. They found a significant reduction in alpha and an increase in delta activity both with natural and sedated sleep. Hypnotic agents reduced the incidence of movements during sleep and the number of times sleep
became shallow. They also consistently depressed blood pressure, heart rate and respiratory rate in normal subjects (Meyers, Cook and Page, 1940). Psycho-physiological tests in which the patient is required to perform some mental exercise are capable of measurement but suffer from the effects of a number of uncontrolled variables such as intelligence, motivation, environmental conditions and the facilitation produced by practice. Even in trained volunteers, six out of ten tests including the visual reaction time failed to show the effects of a barbiturate (Goodnow et al., 1951). They will clearly be less effective in hospital patients.

During sleep the skin resistance is high due to diminished sweat gland activity (Hawkins et al., 1962).

It is clear, therefore, that there are many ways in which objective measurements of anxiety and sleep can be obtained. While each of the tests described will contribute information which is of value in classifying the patients, none of the individual tests alone is specific for anxiety or sleep. For example, changes in the heart rate may be due to a variety of causes encountered in anaesthetic practice, while atropine diminishes the galvanic skin response.

When using objective signs as a measure of a subjective response it is, therefore, customary to use a battery of tests and to consider together the findings from all the tests. This is most easily done by awarding points in each test to the results which are suggestive of the condition being sought, in this case sedation, and withholding points where the results suggest anxiety. In this way a score is obtained which should represent the overall degree of sedation present as indicated by all the tests employed.

SCORING SYSTEMS

Scoring systems involving the allocation of points to the various responses which contribute to the total score obtained in an individual patient have been used in the study of drugs used in premedication (Smith and Jeffries, 1959; Dundee, Moore and Nicholl, 1962). Such methods were used by these authors to study not only the sedation produced but also circulatory and respiratory depression and other side effects.

In devising such a system there are a number of factors to be considered. The tests employed must be carefully selected so that they are not influenced by factors inherent in the circumstances of the experiment. In addition they should be capable of giving reliable results under the practical conditions of the test. Ideally they should be so selected that they are easily quantifiable, that is a greater change in the variable measured should reflect a greater degree of anxiety or sedation.

Careful consideration must be given to the allocation of points to results of individual tests. The number of points which can be justifiably awarded to any one result will depend on the extent to which the test contributes to the measurement of the parameter which is being studied, in this case sedation. For example electroencephalographic evidence of sleep would be a strong indication of good sedation and would thus merit a fairly generous allocation of points; whereas a prolongation of reaction time might indicate the presence of drug-induced sedation or alternatively could reflect the changes brought about by anxiety (Hendry, Norris and Nisbet, 1963) and would not merit as large an allocation of points. Undue weighting of any one reading may thus unbalance the total score and give a false result.

In compiling a scoring system Doughty (1959) has pointed out that it is essential to have an "ideal patient" in mind. Such a patient should obtain the maximum score available from the points allocated. He has further shown that from the data available in any one experiment, it is possible to obtain varying results when the criteria for the "ideal" patient are altered. At the beginning of any work involving a scoring system the desirable features which are being sought should, therefore, be clearly stated.

Even when careful attention is given to these points there are obvious disadvantages in a system which uses a number of tests each involving a possible error, no matter how small. When, however, a large number of tests are used and the allocation of points to each has been correct, it should be possible to obtain from a scoring system a broader, more reliable, picture of the degree of sedation obtained than is possible by considering only one or two factors. In the latter case the presence of any error will produce a much larger distortion of the results.
THE SEDATION AND SLEEP THRESHOLDS

We have so far discussed methods of measuring the degree of change produced by a given dose of drugs in a particular patient. A different approach to the measurement of drug effect has been used by Shagass (1956), using what he describes as the “sedation threshold”. He gives intravenously to his patients measured doses of amylobarbitone at regular intervals until speech is slurred and characteristic electroencephalographic changes are found. The amount of drug required to produce this end point is measured and this is defined as the “sedation threshold”. Shagass and Kerenyi (1958) have extended this method to measure the amount of drug required to induce sleep; sleep being defined as a point at which the patient ceases to respond to verbal stimulation by repeating certain phrases. These methods, valuable as they are in certain types of work, are of limited value to the anaesthetist studying premedication.

ELIMINATION OF VARIABLES AND ANALYSIS OF DATA

Before significance is attached to changes in a physiological function which may vary, the circumstances of the experiment must be such as would reduce all other variables to a minimum. This means that the patients are selected preferably from the same sex and as far as possible from the same age group. They should not suffer from any disease likely to influence the trial. It is usual to exclude from such a trial patients showing symptoms or signs of a disease other than that for which they are under treatment.

Drugs which are to be studied should be given in a random fashion, using either random tables or selecting numbers from a hat and giving numbered ampoules accordingly. Neither the patient nor the anaesthetist nor any other person concerned in the trial should have any knowledge of what drug is being studied at the time of the experiment. The data collected should be measured accurately and recorded at the time of the experiment. When patients in a series are to be used as controls they should be studied under the same conditions as those who are given the trial drugs. This means that they should be studied during the same period as the patients undergoing the trial, lest time has altered imperceptibly the techniques which are being used. Where two or more drugs are to be compared, the same considerations apply.

It is an advantage to study patients from a one-ward unit and to use the same anaesthetic room in an investigation of drugs in premedication. This reduces many of the variables which may arise due to differences in nursing technique, personnel and environmental conditions.

The pharmacological effects of drugs vary with the mode of administration. Where a comparative trial is in progress the drugs must be administered by the same route, in effective doses and preferably in equipotent doses. It is difficult to establish equipotency in human beings without resorting to methods similar to those described for the measurement of the “sedation threshold”. Equipotency may be established in animal experiments, but in view of species variations the results are not necessarily applicable to clinical work.

Sometimes an attempt is made to administer drugs on the basis of body weight. Total body weight, however, is the sum of lean body mass and adipose tissue. The proportion of these two types of tissue varies considerably in different individuals and the total body weight, therefore, does not necessarily form a valid basis for administration of sedative drugs.

Absorption of drugs given by mouth is variable, as is absorption following subcutaneous injection. Injection of a drug intramuscularly depends on the technique of the nurse concerned. While the most constant results are obtained by intravenous injection, and this is the route chosen for a pharmacological study in animals, premedication is seldom given clinically in this way. Thus the effects obtained may not correspond to those in clinical practice and many investigators feel that a clinical problem should be studied using the techniques which are appropriate to clinical practice.

The potency of different batches of drugs under investigation must usually be assumed to be constant. Fortunately, little difficulty arises in testing standard sedative drugs, although drugs in solution may deteriorate on storage. When new drugs are being investigated the possibility of variation in potency from batch to batch may arise.
Statistical analysis.

In designing a trial and analyzing the data obtained from it, the anaesthetist will normally seek the help of a statistician. He will advise on the statistical tests most appropriate to the type of trial envisaged, but the clinician is responsible for the control of the clinical variables which have been outlined above.

Analysis of the results obtained from a scoring system involves a comparison of scores obtained from a number of different tests in a number of different patients. If the variables discussed have been eliminated and the tests have been chosen on valid clinical grounds, the same score in different patients should represent the same degree of sedation. However, the final score may comprise positive results from different tests in the individual patients. As an example, let it be assumed that two patients undergo three different tests, A, B and C. Both patients could obtain a score of 2 out of 3 but they could derive their points from A and B or A and C or B and C. If the weighting placed on each test is correct then the points obtained from A=B=C and therefore A+B=A+C=B+C. As all scoring systems are built up to some extent in an arbitrary fashion (Smith and Jeffries, 1959; Dundee, Moore and Nicholl, 1962) it is not always possible to ensure that the sum of the clinical tests A+B=C and any form of statistical analysis of the results obtained may be open to this objection.

The simplest method of analysis of the results obtained in a trial involving two groups of patients is to apply the Student “t” test to the mean scores in each group. Dundee, Moore and Nicholl (1962) object to this method of analysis since “the assignment of a score to a particular finding (even though this be done on valid clinical grounds) has the disadvantage that the mean score of the series is meaningless as regards the ability to compare it statistically with the mean value in another series”. This objection is raised because of the difficulties we have discussed earlier where the total score is composed of positive results from a number of different tests.

These difficulties may to some extent be overcome by studying the scores in groups. Thus, if the total possible score is 10, scores 0 to 4 may be considered poor, 5 and 6 as fair, and 7 to 10 showing good sedation. In this way the chi-squared test can be applied to the groups showing good, fair, and poor sedation. Provided these groups are fairly large it is possible to avoid “null cells” where no patients occur in any one group. Unfortunately this method has the disadvantage that in constituting the groups “poor”, “fair” or “good”, a small error in total score, as for instance from 4 to 5, can result in the patient being placed in the wrong group.

Both the “t” test and the chi-squared test have been used in a study to be reported (Nisbet and Norris, 1963) and the correlation between the results obtained is good. This does not necessarily mean that the tests are equally applicable.

A method which is gaining increasing popularity is the ridit analysis. The application of this method has been described by Bross (1958) and its use is advocated by Dundee, Moore and Nicholl (1962). The advantages of the method and its application are described in an appendix to their article.

It can be seen that there are many difficulties in the analysis of the data obtained from clinical trials and the subject is dealt with by Mosteller in Beecher’s book The Measurement of Subjective Responses (1959).

DISCUSSION

Most studies of premedication involve the investigation of a multiplicity of effects. However, unless it can first be shown that a drug used will produce good sedation the study of the other effects is of little value.

Beecher (1959) has summarized much evidence which shows that most subjective states can be measured by using certain objective signs. The main advantage of such objective tests is that they can be quantified and are of value in comparing the effects of different drugs. A large variety of tests is now available and may be incorporated into a scoring system. These scoring systems are necessarily of an arbitrary nature but the contribution of each individual test to the total score can be checked by correlating the results of the individual tests against the total scores obtained. Any test which shows poor correlation can then be subjected to further studies and if necessary rejected. Many of the problems involved in selecting which tests are of greatest value and in determining the weighting to be attached to each test in its contribution to
the total score can be determined only by experience and in the long run by trial and error. To this end the system should be used first to test the effects of drugs whose actions are well recognized in clinical practice. A valid system should be able to distinguish between sedatives of known potency and the results for each drug should be reproducible, preferably in groups which contain relatively small numbers of patients.

It is recognized that in the population as a whole the number of placebo reactors is high. Thus in any group of patients studied the number of good results obtained with a sedative will include a proportion of placebo reactors. Such reactors are difficult to detect by any means other than direct administration of a placebo.

Where the comparative effects of a drug relative to standard drugs are to be studied, the placebo effect should be constant. If the absolute value of a drug is to be established, it must be compared with a placebo and also with the effect of no drug at all.

It is hoped to report studies using a scoring system based on simple clinical tests and to study in greater detail the application of more complicated methods to the problems of objective measurement of sedation.

REFERENCES

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APPRECIATION DE LA SÉDATION PREOPÉRATOIRE PAR DES "MESURES" OBJECTIVES

1: INTRODUCTION: CONSIDERATIONS GÉNÉRALES

Sommaire