CLINICAL EVALUATION OF MILD ANALGESICS

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- 1 Mild analgesics pose particular problems in evaluation because of difficulty in getting suitable patients, the frequent use of oral administration and their long-term use.
- 2 Despite their limitations it is possible to quantify both pain severity and pain relief using either 'pain scores' or 'visual analogues'.
- 3 A trained observer can add information in addition to the patient's interpretation of pain.
- 4 There are particular problems using crossover studies with analgesics and the sequential method of evaluating results is not as useful with mild analgesics as with more potent drugs.
- 5 Opinions differ as to the importance of dummy medication in the study of analgesic drugs; difficulties may arise from ethical as well as practical reasons.
- 6 In the overall evaluation of mild analgesics it is important to consider their long term side effects.
- 7 Access to a large number of patients with a constant pain of 6–8 h duration and a smaller number with long-term pain is the most important prerequisite in the evaluation of mild analgesic drugs.

Introduction

There have been many reviews on "Measurement of Pain", which is closely related to the evaluation of analgesics. However, most deal with experimentally produced pain and with animal experiments. This communication deals with practical aspects of assessing both the efficacy and side-effects of mild analgesics.

By definition mild analgesics have the potency of aspirin and phenacetin and are more frequently given by mouth than parenterally. Furthermore their administration is often on a long-term basis. All of these influence the methods of evaluation and raise practical and even ethical problems. As an example, postoperative pain is a valuable and constant stimulus against which one can assess the efficacy of potent analgesics (Beecher, 1956; 1957; 1959; Gupta & Dundee, 1974a; 1974b). Such studies are ethical, and can be carried out with drugs given intravenously or intramuscularly, but are of limited use for mild oral analgesics. The latter can, however, be studied in patients undergoing body surface operations (Grainger, Gawley & Dundee, 1977).

The oral route poses problems of ability to swallow, absorption and the occurrence of vomiting and nausea, either pre-existing or caused by the drug. These again are limiting factors in the study of postoperative pain. The nature of the analgesic, its pK_a , dissolution characteristics and any effect it may

have on gastric emptying will obviously affect efficacy. With a new preparation one would like to give the initial dose intravenously to ensure that absence of efficacy is not due to absence of drug at receptors, but this is often not possible with mild analgesics.

The long-term use of mild analgesics, which is their main field of usefulness, poses problems of gastric intolerance, acquired tolerance, interactions with other agents, and toxicity. Either or all of these could affect the clinical use of an otherwise useful analgesic and have to be taken into consideration.

Patients for study

The investigator must be satisfied with the potential analgesic action of the drugs as shown in animals. The study should have the approval of a local ethical committee and in certain cases permission from the statutory regulatory body. In addition the permission of the patient is essential with completely new drugs, but in comparisons of established drugs or a dose-response study, this may be dispensed with. Other patient safeguards are discussed later.

Patients are required who have pain of moderate severity from which spontaneous remission is unlikely to occur within a period of 6–8 hours.

Severe		3	D
Moderate		2	C
Mild		1	B
Nil		0	A

Figure 1 Pain scores (after Keele, 1948) ranking of pain severity both by patient and observer.

Ideally some subjects should have chronic pain of constant severity which is expected to last for a period of 4–6 weeks. The ethical and other limits of using postoperative pain have been discussed and will be referred to later. In practice patients having body surface operations form a discrete useful group. Anaesthesia can be with techniques that do not require parenteral analgesics and the incidence of postoperative vomiting is low.

Other types of chronic pain may be used for long-term therapy but we have the difficult problem of 'pain as an old friend', to which the patient has become resigned and which is a major focus for all their interests. The reaction component of pain has dominated the actual pain stimulus. However, arthritic and similar pains can be used for study of mild analgesics and they may be particularly useful for evaluation of anti-inflammatory agents.

From bitter experience the author would advise against the use of regular recurring pain, such as dysmenorrhoea, as the sole means of assessing analgesics. Even with an antispasmodic agent which may be specifically indicated in this condition, there can be problems from variability of pain and emotional overlay. Such a study should be combined with more conventional ones.

Measurement of pain

This includes measurement of pain relief by comparing the efficacy of analgesics. It is difficult to agree wholly with Huskisson (1974) that pain cannot be said to have been relieved unless "pain or pain relief have been directly measured". Pain is a subjective feeling, which is beyond absolute analysis — it is "what I feel, what hurts me and how much it hurts me". However, numerals can be assigned to feelings and used as conventions to describe their severity (Stevens, 1946). But it is appreciated that no final judgement on their validity can be given — validity can only be relative and examined by empirical comparison (Aitken, 1969). This is the basis for the clinical methods used in the so-called measurement of pain. Assuming that the untreated pain remains constant for a reasonable period of time, a number of approaches can be adopted.

Numerical or descriptive ratings

These were popularized by Keele (1948) and called "pain scores". The original scheme gave grades to which numbers could be attached. Letters might have been a better choice for grading severity (Figure 1) as they would have eliminated the tendency to apply parametric statistical methods to the findings. This does not mean that the average score of a series is meaningless — it does mean that the standard deviation (S.E.) or non-parametric data should not be used for the conventional Student *t* test. The average score, whether of pain severity or pain relief, indicates trends and will show up large differences between drugs, or between active drugs and inert preparations. It probably should not be used for small differences, as used by Parkhouse, Pleuvry & Rees (1979). Alternatively, and more ideally, scores can be grouped and analyzed using the χ^2 method or a riddit (Bross, 1958) or another transformation is carried out. Grouping necessitates fairly large numbers of patients and perhaps one or more grades may have to be pooled for statistical analysis.

Pain scores can be compared at predetermined times after drug administration, or they can be totalled over a fixed period, or they can be used to determine an "all or none" response — relief, inadequate relief, some relief, or no relief. The choice of method will depend on the number of patients, the nature of the study and the appearance of the crude data. It is not possible to be dogmatic concerning numbers in planning a study, particularly with mild analgesics.

A very helpful refinement of the pain scores method is to use both patient and trained observer data. The patient bases his opinion on personal experience (how I feel), whereas the trained observer's estimate is based on signs of discomfort, that is, external evidence of severity. Here it is important to specify exactly what will be taken as severe, mild, and so on, by the observer; such a classification, used for postoperative pain is shown in Table 1. In practice, the continuous assessment of pain and allocation of scores is repetitive and can become very boring. Despite this,

Table 1 Grading scheme for pain severity

Patient estimate	Pain score	Observer estimate
Very severe	5	Patient writing, sweating and distressed
Severe	4	Patient with strained facial expression
Moderate	3	Patient still, eyes closed and avoiding movement
Slight	2	Patient dozing or asleep
None	1	No discomfort, patient completely at ease

Figure 2 Four forms of visual analogues for rating pain severity.

the number of observers must be limited. Some will use physicians as observers (Gupta & Dundee, 1974a; 1974b), whereas others prefer trained nurses (Parkhouse & Holmes, 1963; Parkhouse, Pleuvry & Rees, 1979).

Relief or severity

These descriptive ratings can of course be applied to pain relief as well as to pain severity and this may be more relevant in the study of analgesics. This however implies that the initial pain severity is similar — as far as can be assessed clinically — in all cases studied. It also implies that pain relief is in fact relief of pain and not ease of mental anguish, discomfort, distension or sickness or other factors which distress the patient. Perhaps more use should be made of the total patient feeling and the patient's overall improvement. So often, 'relief of pain' is found following the administration of a non-analgesic tranquillizer. Provided we have satisfied the patients we have achieved our goal.

Visual analogues

These have been popularized by Huskisson (1974) and Figure 2 shows four possible types. The patient is asked to indicate the pain severity on a line which may be marked at intervals or be completely plain. In Figure 2 the use of marks at 'mild', 'moderate' and 'severe' really converts this into pain score approach and most patients will put their mark at one or other of the five possible grades. The tendency is less in the bottom example where the letters are spread over the length of the scale. With 20 marks to indicate divisions (top example) patients are again inclined to use the 5, 10 and 15 positions to the exclusion of intermediate positions.

There is no objection in showing patients where they placed their mark on a previous occasion but the line should not be presented horizontally on one occasion and vertically at the next. Visual analogues can also be used to indicate pain relief and again the plain line is preferable.

Other tests

These are widely used in the assessment of potent analgesics; for example, FEV₁ or tidal volume following operation can be affected by analgesics (Loan, 1969; Loan & Dundee, 1967a; 1967b; Masson, 1964). However, these tests are of little value with mild analgesics. In specific instances increased movements (of joints and limbs) can be used to indicate greater degrees of pain relief, but this does not apply to all drugs or in all circumstances. It is also an indication of the efficacy of an anti-inflammatory drug but not a measure of analgesia *per se*.

Elimination of bias

Both pain scores and the use of visual analogues are open to bias and this must be eliminated as far as possible. The need for this is obvious and implies the use of randomization and double-blind techniques. However, there are a number of simpler factors which are often forgotten and which, in practice, can have a profound effect on the outcome of a study, particularly with mild analgesics where there are not great differences in drug action. Both the patient and the observer can be influenced by foreknowledge of the drug (or drugs) to be given and by preconceived ideas of the efficacy (or lack of efficacy). The patient can be affected by its form of presentation and the manner in which its efficacy is elicited and also by casual comments — usually unwitting — by attendants or other patients. Attendants must either be fully aware of the nature of the study and the need to eliminate bias, or completely unaware that a study is going on; a half-way approach leads to insatiable curiosity or antagonism at not being consulted.

Similarly, randomization is not as simple as it seems. It must be done by truly random numbers and allocations prepared by persons other than those concerned with the administration or the assessment. It does of necessity embody the 'double-blind trial concept' in which neither the subject nor the assessor knows the actual drug which has been given, but it is wise to assure the patient that a code is readily

available and that it will be broken in the event of an unexpected happening. When pain is fairly severe and a placebo is included in the study, most workers will insist on breaking the code if relief is not obtained within a reasonable period of time. This is essential in postoperative pain and it is unethical not to include such a clause in the protocol. Nursing staff and other attendants will certainly want it.

Complex routines may be required for the double-blind administration of physically dissimilar drugs and ideally these involve a third person who prepares and administers this therapy according to the usual principles of randomization. As the intravenous route results in a different profile of drug effect, such as earlier onset and greater initial toxicity, it is difficult to include it in randomized trials involving oral and/or intramuscular routes of administration. However, the latter can be simply combined by giving either: intramuscularly inert, orally active; intramuscularly inert, orally inert; intramuscularly active, orally inert.

Design of studies

A full discussion of this is not warranted as it is dealt with very adequately in standard textbooks, monographs, clinical trials, journals, and more recently in a continuing series (Wright & Haybittle, 1979a, b and c). Generally speaking, evaluation of any analgesic is based on the 'before and after' type of study, that is, pain severity before and after administration of the drug. This allows one to study the onset time and duration of action of single doses, an exercise which is essential before proceeding to long-term studies. Such evaluations are usually carried out at more than one dose level and are usually based on a logarithmic increase such as 25, 50 and 100 mg, and where possible should be combined with measurement of plasma drug concentrations. They also involve a standard compound, usually given in its accepted effective dose; and by suitable plotting of effects it is possible to determine equivalent doses. Difficulties arise with compounds of differing pharmacokinetic profile — slow onset and prolonged action compared with a rapid transient action — and each of these has to be met when they arise.

The long-term use of analgesics is the next logical step but this must be preceded by single dose studies. Here plasma drug concentrations are even more desirable, to detect cumulative effects. Side-effects are more likely to occur with prolonged treatment; and, particularly in early cases, it is desirable to carry out suitable laboratory investigations designed to detect organ toxicity. Repeated evaluation of pain relief is not so necessary except to detect the occurrence of tolerance and interaction with other medications. If there is either a dramatic improvement or worsening in analgesia one should look at the

patient's condition rather than adjust the dosage. There is no way in which one can foresee all the problems in long-term use of mild analgesics; each patient must be seen frequently and the efficacy and side-effects noted. In practice one often dispenses with pain scores or visual analogues after a few days, but perhaps this is wrong. The most important thing is a detailed record of the effects attributable to the drugs, irrespective of how this is recorded.

Crossover study

In this the patient is used as his own control (before and after study) but as in so many aspects of the measurement of pain this is not as simple as it seems. Supposing drug A is followed by drug B and the patient reports a more beneficial effect from the latter, this could be due to (1) a greater potency of B compared with A; (2) a diminution of pain severity; (3) residual analgesic effect of A enhancing the action of B; or (4) effect of A in altering response to pain, for example, decreasing apprehension or causing drowsiness. These problems will be greater with prolonged use of oral drugs, or where there is a short time interval between single administrations. Ideally pain should have returned to the same severity after A before B is given but this is clearly not always practical or, more important, it may even be unethical.

Sequential studies

Because of their insensitivity these are of limited value in the assessment of mild analgesics. It is not only difficult to get a pair of patients with a similar degree of pain, but it is more difficult to give a preference for one or other test drug. In one such study I have finished with 16 out of 21 patients being 'tied pairs', that is, i.e. no clear distinction between effects whether these were success:success or fail:fail. A concomitant pain score 'before and after' trial did, however, reveal a slight, but clinically significant, difference between the two drugs.

Use of dummy medication

The term 'dummy medication' is preferred to 'placebo' as one is not purposely giving a drug to 'please the patient'. One is seeking to establish the background level of improvement which may be expected without any specific pharmacological effect, for example, the beneficial effect of assurance and attention coupled with the personality of the observer. The importance of this latter cannot be overstressed in analgesic studies; in similar types of observations of pre-anaesthetic medication I have found quite a differing 'placebo response' with differing observers. This is a good reason for limiting the number of people involved as far as is practically possible.

Dummy medication is also essential in testing whether the method of study can detect significant drug effects. In practice, a drug with an effect indistinguishable from that of a similar inert preparation is of no clinical value. Before discarding such a drug, particularly if it is a non-toxic compound with promising efficacy in animals experiments, one should ensure that the method of study is sufficiently sensitive to distinguish between an active and inactive compound. This latter can be resolved by the inclusion of a known active compound in the study.

The ethics of inclusion of an inert preparation in the study of analgesics is a controversial subject. The problems can be lessened by: (a) inclusion of a 'failure of therapy' clause in the protocol, the key being broken if the pain is not relieved within a specific time; (b) a full explanation of what is involved, both to the patient and more important to the nursing staff, other attendants and the relatives; (c) pointing out that if one is going to give a new form of treatment with its potential risks, albeit very small, then the findings should be of value (this may only be achieved by the use of a placebo).

The local situation with reference to ethical committees, the attitudes of one's colleagues and the views of the physician in charge of the patients will also affect the use of a dummy preparation. Each study will have to be considered on its merits as will each individual patient.

Other ethical problems

The decision to change a patient on long-term analgesic therapy who is getting adequate pain

relief to a new analgesic is one that cannot be taken lightly. The reverse situation arises where the test drug in the first dosage administered is providing good pain relief; here it is difficult to reduce dosage for the purpose of a dose-response curve, or even change to the standard preparation.

Continuation of treatment in the presence of troublesome side-effects also raises ethical problems, as does the use of anti-emetics and anti-anxiety drugs which may affect the patient's response to pain.

Side-effects

These cannot be discussed in detail, but they should be noted and their severity assessed as for any other new drug. Vomiting and nausea will be the most common occurrence, and their relationship to dosage, sex of patient, ambulation, and so on must be considered (Dundee, 1977a; 1977b). Equally important is the ease with which side-effects can be controlled and the influence of anti-emetics on analgesia and sedation.

Constipation is the other side-effect which should be sought, particularly with long-term therapy. Here again the ease of alleviation is important. It is unlikely that addiction will be a problem with long term use of mild analgesics, but habituation may occur.

In the light of the toxic effects of long-term use of mild analgesics, patients receiving new drugs should be screened periodically for evidence of renal and liver dysfunction, and blood should be examined for evidence of toxicity.

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Discussion

DR SWERDLOW recommended the use of two different doses in a trial as a way of confirming the sensitivity of the method.

PROFESSOR DUNDEE said that he normally suggested the use of three doses chosen on a logarithmic basis for this purpose.

DR SWERDLOW considered analogue scales difficult to use. Patients required much explanation, were uncertain often how to grade the severity of their pain and frequently became introspective. Dr Würz agreed and added that analogue scales were sometimes regarded by patients as intelligence tests.

PROFESSOR DUNDEE'S experience, however, was that 90% of patients could comply with analogue scales, although perhaps they were easier to use in younger patients. He admitted that one needed patience to use the scales properly.

DR STRUPPLER quoted Huskisson's opinion that subsequent assessments using visual analogue scales

should be made with the previous assessment available to remind the patient of how he felt before treatment.

DR PRESCOTT emphasized the importance of kinetic considerations in testing analgesics, and pointed out that where a drug possessed a long half-life the concentration achieved after a single dose might be subtherapeutic. He cited propoxyphene as a possible example. In single-dose studies it was not shown to be a potent analgesic, yet in practice it was a very popular pain reliever.

DR WÜRZ said that it was important to differentiate acute and chronic pain states. Acute pain was nearly always somatic. In chronic pain, personality disorders and psychiatric disturbances played a more important role. He regarded chronic pain as falling into one of four categories. Firstly, somatic pain; secondly psychosomatic pain, where somatic factors coincided with personality disorders or reactive states; thirdly endogenous pain, arising in endogenous depression or schizophrenia; and fourthly psychogenic pain. He thought this classification had implications for therapy.