Opioid Agonist/ Antagonist Drugs in Clinical Practice

Proceedings of a Symposium
Torquay - 28th September, 1983

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Preface

N-allylnorcodeine, the first opioid antagonist, was synthesized in 1914 by J. Pohl. This drug was manufactured in an attempt to improve the analgesic properties of codeine; however, it was subsequently found to antagonize both the respiratory depression and hypnosis induced by morphine. In addition, large doses produced an excitatory effect.

Some 25 years later, McCawley and his colleagues (1941) synthesized *N*-allylnormorphine (nalorphine) in an attempt to produce a compound which would reduce the respiratory depressant and other adverse effects of an analgesic dose of morphine. Following purification of the substance by Weijlard and Erickson in 1942, it was observed that strong antagonism existed to almost all of the actions of morphine.

Because of its use in the therapy of morphine overdosage and its lack of physical addictive properties, nalorphine provided the stimulus for the synthesis of a large range of opioid antagonists with varying degrees of agonist and antagonist potency. With the recent description of endogenous opioid receptors of different types and specificities, a major impetus has been given to research directed towards development of a strong pain-relieving agent without abuse potential or other undesirable side-effects.

This volume records the proceedings of a symposium held in September, 1983, and devoted to the place of opioid agonist/antagonist drugs in clinical practice. The symposium was in three parts. In the first, there was a review of methods of pain relief and assessment of analgesic efficacy in addition to a description of the endogenous opioids, opioid receptors and opioid pharmacokinetics. Secondly, the uses, constraints and limitations of currently used opioid drugs in clinical practice were covered. The most recently introduced opioid agonist/antagonist in the U.K. is nalbuphine and the third part of the symposium was devoted to the potential advantages and uses of this compound.

The editors hope that the publication of these proceedings will result in a

text which is a valuable update on the treatment of pain and on possible future progress in the pharmacology of pain therapy.

We are grateful to Du Pont Pharmaceuticals, who financed the symposium and this publication.

Walter S. Nimmo, Glasgow
Graham Smith, Leicester

November, 1983

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Session III: Clinical use of nalbuphine

Session I: Pain and the opioids

Pain – a general perspective

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Summary

Currently, the management of pain, both acute and chronic, is poor for a variety of reasons, including difficulty in defining and measuring pain, production of side-effects with systemic analgesic drugs and widespread individual variations in accompanying psychological components and analgesia requirements.

Many studies of pain and the efficacy of analgesia fail to follow the strict criteria (double-blind technique, use of placebos and/or reference standard, etc.) enumerated as long ago as 1955 by Beecher.

There is still no satisfactory method for the measurement of pain, and of the techniques used (e.g., respiratory function tests, urinary excretion and plasma concentrations of catecholamines, plasma cortisol levels, subjective scoring, etc.) the linear analogue score is probably the most useful despite its subjective nature. Very recently, it has been suggested that the total analgesic dosage used with self-administration systems may be a good index of the degree of pain experienced by the patient and the technique has been shown to be useful in defining equi-analgesic doses of differing drugs. The intravenous use of analgesic drugs by self-administration systems has been found to be associated with relatively constant plasma concentrations of the drugs; lower doses may be utilized than are available with intramuscular prescriptions. Rate control systems have also permitted the demonstration, more recently, of the minimum analgesic plasma concentration for different drugs.

Introduction

Pain is an extraordinarily complex sensation which may be described broadly

as an integration of three components: afferent nociceptive stimulation, interpretation of these signals by higher centres (involving previous experience and memory) and an emotive or affective component. Unfortunately, the sensation may be generated by the subject himself without any obvious external stimulation. However, it is difficult to sub-divide pain into physical or mental classifications and it is preferable to regard it as a spectrum comprising conscious discomfort, autonomic changes and emotional qualities embracing fear and depression.

Most pain encountered clinically is transitory and it may be mild or severe, e.g., postoperative pain. Occasionally the pain becomes chronic and intractable. Patients with chronic pain generally present with either terminal disease or a normal life expectancy. Treatment is generally easier in the former than the latter category.

Clearly, there are obvious differences in the extent of each of the three major components of pain (nociceptive stimulation, interpretation and affective or emotional components) in acute mild, acute severe, chronic temporary and chronic permanent types of pain. The problem is compounded further by the fact that when obvious stimulation of nociceptors exists, central transmission of the information may follow different pathways. Acute intermittent pain is transmitted by Aδ fibres via the spinothalamic tract while continuous pain is transmitted by C fibres via the spinoreticular system. Wallace and Norris described two types of postoperative pain: a dull steady pain occurring at rest and a sharp stabbing pain on movement, the former being more responsive to morphine [1].

Experimental pain is used in the laboratory for testing analgesic drugs. Many tests exist which use experimental animals (e.g., tail flick, jump-flinch, etc.); these are useful for preliminary screening purposes. For humans, a variety of experimental methods has been employed, including the use of heat to specific areas of the body [2], cold immersion of the hand [3], tibial pressure algesimetry, ischaemic pain induced by standard muscle activity in the presence of vascular occlusion [4], electrical stimulation of the skin or dental pulp [5] and injection of chemicals to produce inflammatory reactions [6].

Although these techniques possess the advantage that standardization may be applied with respect to the stimulus and racial, social and ethnic origins of the subjects, it is obvious that, in these tests, two of the three major components of pain (interpretive and affective) will vary considerably in degree from that experienced during pathologically-induced pain.

The purpose of this paper is to review briefly problems encountered in the clinical study, treatment and measurement of pain. This is an enormous field and the discussion which follows pertains mainly to the acute severe type of

pain. Further information may be obtained by reference to recent publications (e.g., [7–10]).

Treatment of pain

Treatment of acute pain requires attention to suppression of afferent nociceptive stimulation at either peripheral or central sites, suppression of autonomic accompaniments to painful stimuli and therapy for the affective component. Different modes of therapy have different efficacies at these sites, the most obvious example being local anaesthetic techniques, which fall outside the scope of this paper.

Therapy of pain with systemic opioid drugs is difficult for various reasons, including variation in physiological and psychological factors, and inter-individual variability with respect to the pharmacokinetics, pharmacodynamics and side-effects of the opioids.

Psychological factors which influence the degree of acute pain experienced by patients include social background, cultural beliefs, motivation and the patient's personality. There is a good correlation between the level of anxiety and degree of postoperative pain experienced [11] and also between anxiety levels and changes in pulmonary function tests [12]. There is also a correlation between anxiety levels and degree of neuroticism and it has been shown that patients with higher neuroticism scores exhibit great pain scores after surgery [13].

The importance of therapy for the affective component of pain is emphasized by the observation that psychotherapy reduces the requirements for postoperative analgesia [14] and that diazepam also reduces these requirements [15]. The importance of physiological factors in influencing the extent of pain is demonstrated by variations in the degree of perceived pain for different types of surgery. Classically, patients experience more severe pain following thoracic and upper abdominal surgery than following lower abdominal or peripheral surgery.

There are considerable pharmacokinetic variations in response to differing modes of administration of opioid drugs. Following the i.m. administration of pethidine, it has been demonstrated that there may be a two- to five-fold difference in the peak plasma concentration *values* and a three- to seven-fold difference in the *rate* at which they are attained. Furthermore, the plasma concentrations attained do not correlate with bodyweight or lean body mass [16].

Rate control systems for the administration of opioids have revealed marked pharmacodynamic variations. With patient-controlled self-administration i.v. analgesia, variation in plasma concentrations of opioids for

analgesia was 13–44 mg/h for pethidine [17], 30–100 μg/h for fentanyl [18], 0.8–5.1 mg/h for morphine in morbidly obese patients [19] and 0.3–9 mg/h for morphine in patients of normal build [20] following major surgery.

The side-effects produced by currently available opioid analgesic drugs represent a major reason for failure to achieve adequate analgesia, particularly following surgery. Although many of the less serious side-effects (nausea, vomiting, sedation, etc.) prohibit patient acceptance in ambulatory situations, adequate postoperative analgesia is frequently prevented by the more serious side-effects, particularly respiratory depression. Withholding of analgesic drugs by nursing or medical staff for fear of inducing addiction should not be a serious problem as dependence rarely occurs in the treatment of acute severe pain. However, there is no doubt that respiratory depression is the major limiting factor which prevents administration of optimum quantities of analgesic drug. Excellent results may be obtained in the treatment of postoperative pain by continuous intravenous administration of opioids in sufficient dosage. While this is an accepted regimen for patients receiving artificial ventilation, in the spontaneously breathing patient, there is a probability of inducing respiratory depression [21].

A method of reducing, but not totally eliminating, the risk of respiratory depression is by means of a servo-control over the rate of administration of i.v. drugs. The earlier systems involved patient regulated self-administered i.v. bolus doses of analgesia [19, 22, 23].

Hull and Sibbald refined the self-administration i.v. bolus system by combining a low continuous background i.v. infusion with a facility for patient-activated bolus i.v. injections [24]. This system also possesses a negative feedback mechanism to reduce the likelihood of respiratory depression by the use of a mercury-in-rubber pneumograph whereby the system is inhibited if the period between successive inspirations exceeds eight seconds. In addition, the patient is required to press a button twice during a 15-second period before the device is activated.

The use of these machines has been associated with the production of good analgesia (usually better than the average ward regimen for administration of conventional analgesia). It has been found that relatively constant plasma concentrations of drugs are produced [17], that lower doses of drugs are utilized than are made available by intramuscular prescription [22] and that lower doses of drugs may be used than those given to comparable groups receiving intramuscular injections [25]. Despite appreciable variations between patients in the self-administered doses of analgesic (e.g., 10:1), for individuals the rates of analgesic consumption remain relatively constant [26].

In addition to providing superior analgesia to conventional intramuscular

injections, these on-demand systems also offer the possibility of comparing fairly accurately the equi-analgesic doses of different opioid drugs, as well as the opportunity to utilize the rate of drug consumption as an objective index of the degree of pain experienced by the patient (*vide infra*).

Measurement of pain

Because pain is an individual subjective experience, it is extremely difficult to assess its extent by objective quantitative methods. Patient questionnaires are probably the most useful technique. They introduce a widespread opportunity for both subject and observer bias, however. In order to reduce these variables to a minimum, Beecher enumerated the principles which should be incorporated into the design of studies of pain [27]. These comprise:

I. The use of a placebo. Some 30% of the response to morphine, 10 mg i.v., may be a placebo response with a similar time course [28]. Any therapy which is new to a patient must therefore carry a high probability of a placebo effect and this is particularly true of new devices including the self-administration i.v. systems.

II. A double-blind technique. Since the placebo response is so powerful, it is important that any subliminal bias transferred from observer to patient be eliminated. In addition, any subjective bias by a patient conscious of a new mode of therapy must also be eliminated. Unfortunately, it is difficult to maintain a double-blind state throughout the duration of a clinical trial since patients rapidly become aware of the active drug, either by its analgesic effects or by the production of side-effects, e.g., nausea, drowsiness. This is particularly true of self-administered i.v. analgesic regimens, where patients rapidly become aware of some pharmacological actions of the active drug.

III. A crossover design is desirable to reduce inter-individual variation. While this may be feasible for chronic pain, it is more difficult in acute pain, e.g., postoperative pain where the intensity diminishes rapidly over a 24- to 48-hour period.

IV. The use of a reference standard. In studies of acute severe pain, it may be unethical to use a placebo and therefore comparisons should be made against a reference standard. For postoperative pain, the standard is i.m. morphine. However, this introduces problems in maintaining a subject-blind design if i.m. morphine is to be compared against a drug with a markedly different pharmacokinetic profile or where a comparison is made between intramuscular and intravenous forms of administration.