INTERNATIONAL CONGRESS AND SYMPOSIUM SERIES

OPIOIDS— USE AND ABUSE

EDITED BY

J. LEVY and K. BUDD

ROYAL
SOCIETY OF MEDICINE
SERVICES

LONDON NEW YORK

International Congress and Symposium Series
Number 107

Opioids — use and abuse

Edited by
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Royal Society of Medicine Services
London New York
1986

Royal Society of Medicine Services Limited
1 Wimpole Street London W1M 8AE
7 East 60th Street New York NY 10022

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British Library Cataloguing in Publication Data
Opioids—use and abuse (International congress and symposium series; no. 107)
1. Opioid habit
I. Levy, J. II. Budd, K. III. Royal Society of Medicine
IV. Series
616.86'3 RC568.058

ISBN 0-905958-37-3

Editorial and production services by Fisher Duncan Ltd, 10 Barley Mow Passage, London W4 4PH
Phototypeset by Dobbie Typesetting Service, Plymouth, Devon
Printed in Great Britain at the Alden Press, Oxford

Introduction

The old adage that 'practice makes perfect' may hold true in many walks of life. Should the use, over the past 3000 years, of opium and its derivatives be considered, it immediately becomes apparent that even this vast amount of practice has failed to perfect the use of these drugs in the relief of pain.

Such a situation would appear to be a sad commentary upon the way in which the medical profession has failed to heed the lessons learned during those three millennia and how both the teaching and application of this knowledge has failed to furnish patients with an adequate answer to their pain. All too frequently, those who prescribe and administer opioid drugs are unaware of the range of such agents, the spectrum of their properties and their optimal clinical utilization so that full benefit is all too rarely achieved.

In an attempt to engender a better understanding of the opioid drugs, their properties, advantages, disadvantages and nuances of use, a Symposium was organized in Bradford in May, 1985. The speakers were both scientists and clinicians, renowned not only for their specific expertise in the opioid area but also for their skill in presenting knowledge in a readily assimilated form to be easily reproduced for the wellbeing of the patient.

It was a pleasure and privilege to have their contributions to the Bradford Symposium, 'Opioids—Use and Abuse' and I am pleased to acknowledge my debt to all the speakers. Also I would wish to thank my co-chairman, Dr Robert Naylor, Reader in Pharmacology, University of Bradford and my co-editor, Dr Jonathan Levy, the latter particularly for his sterling work with this publication. Lastly but by no means least, might I thank Napp Laboratories for their most generous support of both the Symposium and this publication.

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Mode of action of opioid drugs

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Derivatives of the opium poppy have been used for many hundreds of years for their sedative and analgesic properties. Even today there are no analgesics available which produce a better quality of pain relief. However, since the elucidation of the structure of morphine in 1925, much effort has been expanded to try to produce new chemical entities which retain the good analgesic qualities of morphine but which lack the undesirable properties such as dependence, constipation and respiratory depression. Two discoveries in particular are aiding the search for new opioid analgesics and new treatments for the relief of pain:

(1) The finding that opioid drugs produce their effects by interacting with distinct populations of opioid receptors;

(2) the finding that opioid drugs can act at a number of different sites within the body.

Multiple opioid receptors

Classification of opioid receptors

The first classification of opioid receptors was proposed by Martin and his colleagues (1). They postulated the existence of three opioid receptor types.

(1) the μ-receptor for which morphine was the prototype agonist;

(2) the κ-receptor for which ketocyclazocine and nalorphine were prototype agonists;

(3) the σ-receptor for which N-allylnormetazocine (SKF10 047) was the prototype agonist.

This classification was based on *in vivo* experiments using a dog behavioural model.

Opioid drugs classified as μ-agonists caused depression of nociceptive responses, bradycardia, hypothermia, decreased respiratory rate, indifference to environmental stimuli and, on withdrawal after chronic administration, an intense withdrawal syndrome. Compounds classified as κ-agonists similarly depressed nociceptive

Opioids – use and abuse, edited by J. Levy and K. Budd, 1986: Royal Society of Medicine Services International Congress and Symposium Series No. 107, published by Royal Society of Medicine Services Limited.

responses, but had little effect on pulse rate, body temperature or respiratory rate; behaviourally they were sedative and withdrawal in dependent animals produced a much milder abstinence syndrome than was obtained with the μ-agonists. In contrast, σ-agonists were not antinociceptive but produced tachycardia, hypothermia, increased pulse rate and mania. SKF10 047, the prototype σ-agonist is hallucinogenic in man (2) and it has been suggested that σ-receptor activation is responsible for the psychotomimetic effects that occur with certain opioid analgesics in clinical use, e.g pentazocine. However, the σ-site is not considered an opioid receptor by some because its actions are not reversed by naloxone. It may represent the same entity as the phencyclidine (PCP) receptor which is proposed to mediate the psychotomimetic effects of PCP and related drugs (3,4).

A further receptor type, the δ receptor, was postulated by Lord *et al.* (5) to explain the activity *in vitro* of the endogenous opioid peptides, the enkephalins (6). Thus, methionine and leucine enkephalin were far more potent than morphine in inhibiting twitch responses in the field stimulated isolated mouse vas deferens preparation, whereas the converse was true in guinea-pig ileum. This led to the postulate that, in the mouse vas deferens, enkephalins were interacting with a different receptor from that for morphine and this was called the δ-receptor.

Many independent lines of evidence have established the existence of separate μ-, κ- and δ-opioid receptors. These include binding studies (7,8), pharmacological studies *in vitro* using selective antagonists (9–12), selective tolerance development (13), selective protection against alkylation (14,15) and pharmacological studies *in vivo* (16,17).

Functional correlates of μ-, κ- and δ-receptor activation

All selective δ-agonists currently available are peptides and are thus difficult to use in the whole animal due to problems of rapid metabolism and poor penetration across the blood–brain barrier. Additionally, although some very selective agonists are now available, e.g. D-Pen^2, D-Pen^5-enkephalin (18), none is completely specific and cross-reactivity with the μ receptor may be a problem if large dose levels are given intracerebroventricularly. For these reasons the functional correlates of δ-receptor activation are poorly defined. For example, there is still controversy over the role of δ-receptors in producing antinociception (19–21).

Considerably more is known about the functions associated with μ- and κ-receptor activation (Table 1). Following the pioneering studies of Martin *et al.* (1), considerable

Table 1

Functions associated with activation of μ- and κ-opioid receptors

Action	μ	κ
Analgesia	Strong	Strong
Dependence liability	High	Low
Respiratory depression	Marked	Minimal
Constipation	Marked	Minimal
Cardiovascular depression	Marked	Less marked
Sedation	Moderate	Moderate
Nausea/vomiting	Moderate	?
Dysphoria	No	?

evidence has accumulated to confirm that both μ- and κ-receptors are involved in producing antinociception in animals (22–25). However, μ-receptor activation is also associated with addiction, respiratory depression, cardiovascular depression and constipation. Most strong opioid analgesics in clinical use, e.g. heroin, methadone, pethidine and codeine, are selective μ-receptor agonists and these side-effects are well known problems associated with their use. Such side-effects appear to be much less marked with κ-agonists (1,26–29). Both μ- and κ-agonists produce behavioural depression in animals (1,28,30), and additionally some drugs with κ-agonist properties, e.g. nalorphine and pentazocine, are known to produce dysphoria in man (31–33). Whether this dysphoria is due to κ-receptor activation or another mechanism, such as σ-receptor activation, cannot be resolved until further clinical studies are carried out with κ-agonists. Similarly the question of whether κ-agonists still produce the same degree of nausea and vomiting as μ-agonists must await further studies in man.

Much effort is still being directed towards the discovery of new and more selective opioid agonists in the hope that better analgesic drugs may be produced.

Site of the analgesic action of opioid drugs

The major sites for the analgesic actions of opioid are considered generally to be within the central nervous system, and there is good evidence that both spinal and supraspinal sites are involved. However, evidence is now accumulating that part of the antinociceptive effect of opioid drugs may be mediated peripherally.

Supraspinally mediated antinociception

The major sites for the antinociceptive action of opioid drugs are probably located supraspinally and include the periaqueductal grey (PAG) in the midbrain, and various medullary nuclei of which the most important are the nucleus raphe magnus (NRM), nucleus reticularis gigantocellularis (NRG) and nucleus reticularis paragigantocellularis (NRPG). These are all areas which contain high concentrations of opioid-binding sites (34,35), and where administration of exogenous opioids produces antinociception (36–39). It is thought most likely that administration of opioids into these brain nuclei produces antinociception by activating descending pathways which inhibit the transmission of nociceptive information in the dorsal horn of the spinal cord. There is little evidence for a direct anatomical projection from the PAG to the spinal cord, so it has been suggested that the medullary nuclei are involved as a relay in this pathway (40). Thus efferent projections from the PAG to NRM, NRG and NRPG have been demonstrated by retrograde tracer techniques (41) and physiological evidence corroborates these anatomical findings (42,43). There are descending projections from the medullary nuclei to the spinal cord which travel in the dorsolateral funiculus, the pathway from NRM being largely serotonergic (44), whilst the pathway from NRG/NRPG probably involves noradrenergic systems (45). Recent interest has concentrated on these descending systems as being the primary pathways for supraspinally mediated opioid antinociception. Very much less is known about potential ascending systems, but these may also play a major role.

Spinally mediated antinociception

Noxious information passing along primary afferent fibres is received at the dorsal horn of the spinal cord and relayed to ascending fibres. Thus, blockade of transmission through the dorsal horn is a potential site of action for analgesic drugs and there is now abundant evidence that the spinal cord is an important site of action for opioids. Thus, opioid drugs produce antinociception after intrathecal or epidural administration both in animals (46–48) and man (49), at dose levels which are considerably lower than systemic doses. Within the spinal cord, inhibition of transmission across the primary afferent synapse might be effected in two ways:

(1)a postsynaptic action resulting in hyperpolarization of the membrane of the dorsal horn cell body and hence depression of firing. There is ample evidence for both endogenous and exogenous opioids acting in this way (50–52).

(2) A presynaptic action resulting in a decrease in the amount of released excitatory transmitter. Such an action has been suggested by Jessell and Iversen (53), who demonstrated that the K^+-evoked release of the putative excitatory transmitter, substance P, from slices of rat trigeminal nucleus was inhibited by morphine and opioid peptides in a stereospecific and naloxone-sensitive manner.

Peripherally mediated antinociception

The first indication of a peripheral site of action for opioid drugs came from the work of Ferreira and his colleagues (54,55), who demonstrated a local antinociceptive effect of morphine after intraplantar injection in the rat. Further evidence has come from studies with quaternary opioids which do not pass the blood brain barrier. Thus, Smith *et al.* (56) demonstrated an antinociceptive effect for N-methyl morphine in the acetic acid-induced abdominal constriction test in the mouse, which was reserved by N-methyl nalorphine.

It has been shown that opioid receptors are transported along primary afferent nerves towards the periphery (57) and that opioid drugs inhibit neurogenic plasma extravasation, possibly by reducing release of peptides like substance P from the peripheral terminations of primary afferents (58,59). This has led to the hypothesis that the peripheral antinociceptive effect of opioid drugs is mediated via opioid receptors located on the peripheral terminals of primary afferent fibres.

Elucidation of some of the sites of action of opioid drugs has helped to suggest new therapies for the clinical management of pain. The technique of epidural administration of opioids is now widely employed; and techniques of deep brain stimulation are being pioneered for cases of intractable pain. It is hoped that the further characterization of opioid receptor subtypes will also aid the search for new and better analgesic therapies, the emphasis being on producing drugs which are more selective for receptors other than the μ-receptor.

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Available opiates

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It is well known that the juice of the poppy *Papaver somniferum* provides crude opium from which are extracted the important alkaloids morphine and codeine (and many others). However, chemical derivatives of naturally occurring morphine have been made in laboratories for many years and, more recently, totally synthetic compounds with morphine-like activity have been produced. More recently still, peptides such as enkephalins and endorphins have been discovered and synthesized with the result that it has become necessary to redefine old terms and introduce some new ones.

Opiate

Definition A product specifically derived from the juice of the opium poppy (*Papaver somniferum*), e.g. morphine, codeine.

It should be noted that the term 'opiate' is sometimes applied loosely to morphine derivatives.

Opioid

The word 'opioid' is a new term that has been introduced to cover all those compounds, whatever their chemical type, which possess morphine-like activity but are *not* necessarily derived from the juice of the opium poppy.

Definition A directly acting compound whose effects are stereospecifically antagonized by naloxone. For example, the synthetic morphine-like analgesic pethidine is an opioid.

It should be noted that (i) an opiate is an example of an opioid and (ii) a peptide with opioid properties is known as an 'opioid peptide'.

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Morphine

Morphine is, of course, by definition both an opiate and an opioid and is not only the archetypal compound but is also the reference compound with which all other compounds with morphine-like activity are compared. The actions of morphine can be divided into three groups, namely, those on the central nervous system, peripheral actions and other actions.

Actions on the central nervous system

(1) Depression—analgesia [elevation of pain threshold (small) and of pain tolerance; actions on the dorsal horn and descending inhibitory pathways],
Sedation (which can progress to anaesthesia),
Depression of respiration,
Depression of cough reflex (antitussive action),
Bradycardia with hypotension (minimal except in older patient).
(2) Simulation—mood changes (limbic system),
Euphoria, but occasionally dysphoria. (N.B. In this context the term 'euphoria' is used to mean a sense of peacefulness and not a sense of ecstatic well-being; dysphoria is used to mean the opposite.)
Nausea and vomiting,
Miosis,
Antidiuresis (due to release of antidiuretic hormone, vasopressin),
Sweating,
Central excitation (rare): hallucinations and convulsions.

The remaining actions of morphine are either peripheral actions or other actions of a more general nature.

Peripheral actions

(1) Smooth muscle stimulation:
Gastrointestinal tract: spasm of smooth muscle (including sphincters) with reduced peristalsis resulting in constipation).
(2) Biliary tract: spasm of smooth muscle including sphincter of Oddi,
(3) Histamine release: itching, urticaria, hypotension (with large doses).

Other actions

(1) Dependence: psychic and physical,
(2) Tolerance.

There is no such thing as a perfect drug and morphine is no exception to this rule. Thus, over the years new opiates and opioids have been developed in an attempt to overcome some of the disadvantages of morphine and each of these has its own good and bad points. Before individual drugs are discussed, it is necessary to consider those factors which determine the pharmacological *profile* of a drug and which the

STRUCTURAL FORMULAE OF SOME OPIATES AND OPIOIDS

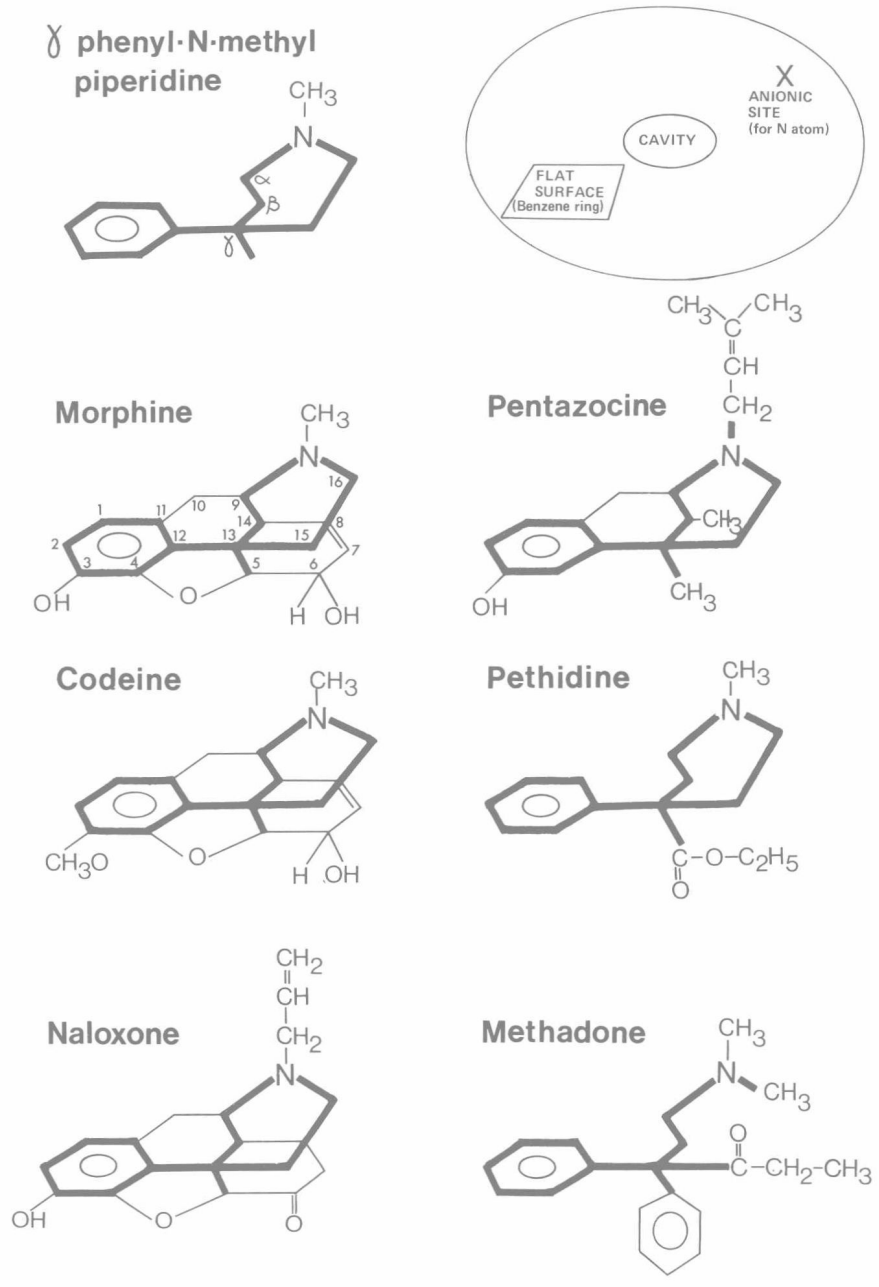

Figure 1. Structural formulae of some opioids. Top left: note that γ-phenyl-N-methyl piperidine forms the common chemical 'backbone' in all the compounds shown, although in some (e.g. methadone) the piperidine ring has been opened. Top right: shows the main features of the opioid receptor as originally described by Beckett and Casy (1). The main topographical features of the receptor are shown and by mentally transposing the formula of pentazocine over the diagram it becomes evident how the main parts of the chemical structure relate to the key areas of the receptor. ©J. W. Thompson and J. G. Walton.