BUPRENORPHINE

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SUMMARY

Buprenorphine is a mixed agonist-antagonist with high affinity at both μ and κ opiate receptors. Its pharmacological profile is determined primarily by partial agonism at μ-receptors and unusually slow kinetics at these receptors. Its intrinsic activity is such that in nearly all clinical situations it is as effective an analgesic as morphine with considerably longer duration and much more favourable acute safety.

In long-term dosing studies in rodents and primates buprenorphine did not produce the manifestations of physical dependence when treatment was stopped. In self-administration studies in the same species only limited levels of reinforcing efficacy were demonstrated when compared with the opiates.

In human former opiate addicts the limited potential of buprenorphine to produce psychological dependence was confirmed as was the favourable physical dependence profile. Some misuse of buprenorphine has been reported in 3 of the 29 countries in which buprenorphine is marketed despite its wide clinical acceptance, particularly as the sublingual formulation.

Key words: Buprenorphine—μ-Receptors—κ-Receptors—Safety—Reinforcing efficacy—Physical dependence profile

INTRODUCTION

"The major characteristics of drugs of abuse are:

(a) they have reinforcing properties that are responsible for at least certain individuals taking them chronically, and
(b) they cause harm to the individual and to society.

Both these characteristics must be fulfilled before a drug can be considered to have an abuse liability or an abuse potential" [1]. To date, all those drugs...
acting at opioid receptors which have been introduced into medical practice as analgesics have been shown to have reinforcing properties. This characteristic of opioid analgesics would not, necessarily, result in abuse since, alone, it is neither socially harmful nor self-destructive. There may be differences in toxicity between drugs of equal reinforcing activity so that their misuse may lead to different levels of harm to the individual. Ultimately, the risk of abuse of an opioid analgesic has to be judged against the therapeutic benefit it offers. In this review these considerations will be applied to buprenorphine*.

Buprenorphine is a member of the C-bridged oripavine series which were synthesized by Bentley and his co-workers [3]. In its structure (Fig. 1) a particular feature is the C₇ side chain containing the t-butyl group. This group occupies a position in space closely corresponding to the phenyl group of the phenyl-alanine moiety of the enkephalins [4] and contributes to the overall lipophilicity of the molecule which has an important influence on its pharmacology.

ANIMAL STUDIES

In rodent analgesic models buprenorphine was a powerful and long-acting antinociceptive agents [5]. In tests where the stimulus was chemical or pressure, it was more than a hundred times more potent than morphine [6]. In heat-stimulus tests buprenorphine was very much less potent being only of about the same potency as morphine, and, unlike morphine, failing to achieve total efficacy. Surprisingly, at the highest dose in the tail-flick test, the antinociceptive effect was reduced almost to zero so that, overall, the dose-response curve was bell-shaped.

Bell-shaped dose-response curves were also shown by buprenorphine for inhibition of gastrointestinal motility [7] and respiratory depression [8] (Fig. 2). The latter is an important consideration in conferring on buprenorphine exceptional acute safety. The LD₅₀-values for buprenorphine were higher than those of pentazocine despite being several hundred times more potent than pentazocine as an analgesic.

*A full review of the pharmacology and abuse potential of buprenorphine has recently been published [2].
The morphine antagonist actions of buprenorphine were demonstrated by reversal of the opiate's antinociceptive actions [5,9] and also by precipitation of abstinence in morphine-dependent animals [5,9–11]. There were species differences in the sensitivity of buprenorphine's antagonist actions so that potency ranged between (0.1–1) times that of naloxone.

Uniquely amongst compounds having significant agonist actions on opioid receptors buprenorphine failed to produce the manifestations of physical dependence when animals were dosed with the drug for long periods (Refs. 11–13; Martin et al., pers. commun.). Neither abrupt withdrawal nor challenge with the pure opiate antagonist naloxone produced an abstinence syndrome. The exception to this generalisation occurred in the spinal dog [14] in which a mild abstinence syndrome was produced.

Animal studies to determine the reinforcing efficacy of buprenorphine have been undertaken by self-administration studies in primates and rodents. Since self-administration was initiated in drug-naive monkeys it is clear that buprenorphine has significant reinforcing efficacy. In a continuous self-administration study in rhesus monkeys which is regarded as highly predictive of human drugs use [11], daily intake of buprenorphine was modest and there were no significant signs of behavioural toxicity. The result of this experiment confirmed buprenorphine's lack of toxicity in the rhesus monkey which was also shown in single dose studies; doses 1000 times the lowest dose (4 μg/kg) causing morphine-like effects, produced no significant toxic symptoms [11]. In comparative terms the self-administration studies indicated that buprenorphine has lower reinforcing efficacy than codeine, pentazocine,
nalbuphine and butorphanol. In the rhesus monkey cross self-administration model [14] buprenorphine showed a lower rate of responding than codeine while in the progressive ratio test in the same species two out of four animals showed higher extinction ratios for pentazocine than for buprenorphine, whilst the other two showed little difference [11]. In a study in baboons [15] buprenorphine showed only marginal rates of self-administration whereas in the same model pentazocine, butorphanol and nalbuphine showed a profile of self-administration equivalent to that of codeine. In morphine post-addict rats, pentazocine, nalbuphine and butorphanol, like morphine, caused relapse to self-administration and, when the drugs were replaced by saline, the rate of self-injection increased rapidly. This behaviour was regarded as indicating psychological dependence potential [16]. In contrast, buprenorphine did not induce self-administration above saline levels (Young and Khazan, pers. commun.).

Most of the more recent preclinical studies with buprenorphine have been in relation to its molecular pharmacology, i.e. its interaction with the subclasses of opioid receptor. The earliest statement on this matter came from Martin [17] who classified buprenorphine as a partial agonist at the morphine (μ) receptor on the basis of his studies in the morphine-dependent spinal dog. He showed that buprenorphine partially suppressed abstinence in the withdrawn animals and partially precipitated abstinence in the non-withdrawn animals. He did not specifically evaluate its interaction with the κ-receptor but from single dose studies of the effect of buprenorphine on various physiological and reflex parameters, he concluded that buprenorphine’s intrinsic activity at the κ-receptor must be low in comparison with its μ activity.

This conclusion is in conflict with those of Tyers et al. [6,18] who studied a number of opioids in a variety of antinociceptive and other tests in rodents. Their conclusion was that buprenorphine’s agonist actions are primarily at the κ-receptor. More direct investigation of the interaction of buprenorphine with opioid receptors suggests that, at both μ and κ receptors, the drug has high affinity and significant intrinsic activity.

A number of isolated animal tissues which have different populations of opioid receptor subtypes may be used to investigate the receptor interactions of opioid drugs. The most commonly used tissues are the guinea pig ileum (μ,κ) and mouse vas deferens (μ,κ,δ); others with more limited populations are the mouse ileum (κ,δ), the rat vas deferens (μ only) and rabbit vas deferens (κ only). Using various combinations of these tissues it is possible to assess the affinities of an opioid by its ability to antagonise specific subtype agonists. Unfortunately since the tissues are not generally sensitive to partial agonists it is very much more difficult to determine the intrinsic activity of a drug such as buprenorphine using these techniques. Binding studies with brain homogenates give similar information concerning receptor affinities but no information about intrinsic activity.

Studies using isolated tissues (Rance and Smith, pers. commun.) (Table I) and binding techniques [19,20] showed that buprenorphine has about equal
TABLE I
ANTAGONIST PROFILE OF BUPRENOPHINE IN ISOLATED TISSUES
Results are mean ± S.E.M. (n = 3).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ke(nM)</th>
<th>vs. D Ala², D-Leu⁵-E (mouse ileum) (δ)</th>
<th>vs. EKC (k) (mouse ileum)</th>
<th>vs. RX783030 (µ) (rat vas deferens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>0.7 ± 0.2</td>
<td></td>
<td>0.072 ± 0.03</td>
<td>0.089 ± 0.009</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>30.8 ± 12</td>
<td></td>
<td>9.4 ± 1.4</td>
<td>0.66 ± 0.14</td>
</tr>
</tbody>
</table>

Affinity for µ- and κ-receptors with about tenfold lower affinity for the δ-receptor. By way of comparison naloxone, a pure opiate antagonist, has highest affinity for µ, with κ and δ roughly an order of magnitude lower [21]. In absolute terms buprenorphine’s affinity is extremely high — between one and two orders of magnitude greater than that of naloxone.

The binding of buprenorphine to opiate receptor subtypes in rat brain has been correlated with the bell-shaped dose-response curve shown in the tail flick test in this species. Dum and Herz [9] showed that at peak analgesic effect (0.5 mg/kg) in vivo saturation of the opiate binding sites occurs. More recently Sadée et al. [20,22] have extended these studies and suggested that in the dose range (0.01–0.5 mg/kg), the agonist effects are generated by interaction with µ and κ-receptors whilst in the antagonist dose range (0.5–10 mg/kg) interaction with δ-receptors are responsible for the observed effect. The bell-shaped dose-response curve may thus be caused by auto-inhibition of the agonist effects mediated by high affinity binding to µ- and κ-receptors by low affinity binding (with low intrinsic activity) to δ-receptors.

Drug discrimination techniques allow the identification of the opioid receptor subtypes at which an opioid has agonist activity. By using as training drugs prototype specific agonists at the individual receptor subtypes the ability of the test opioid to be generalised by the prototype agonists can be observed and intrinsic activity at the receptor subtypes can be identified. Application of these techniques shows that all the antagonist analgesics have some intrinsic activity at both the µ- and κ-receptors. No comparative data on the intrinsic activity at these receptors is available.

Some, but not all, rats trained to discriminate the effects of ethylketocyclazocine (κ-receptor prototype) generalised the effects of buprenorphine [23]. However, since buprenorphine was completely generalised by rats trained to discriminate µ-agonists [24] it was suggested that buprenorphine produces predominantly µ-like discriminative effects. A similar profile was identified for pentazocine [23].

A most important factor in the molecular pharmacology of buprenorphine is the kinetics of its association with, and dissociation from, opioid receptors.
These are illustrated in Fig. 3 which shows the inhibiting actions of the standard agonist normorphine in the guinea pig ileum preparation and for comparison, pentazocine and buprenorphine in the same preparation [24]. Inhibition of the twitch height is achieved promptly by the introduction into the organ bath of normorphine and, to only a slightly lesser extent, by the introduction of pentazocine. Restoration of the twitch height is equally rapidly achieved by antagonism with naloxone. Depression of the twitch by buprenorphine is very much more gradual taking nearly an hour to reach peak effect. Even very high concentrations of naloxone fail to antagonise the effect of buprenorphine and the rate of removal of the drug from the receptor, rather than the presence of the antagonist, is ultimately responsible for the gradual restoration of the twitch.

The tightness of its binding to opioid receptors as manifested in the most unusual receptor kinetics has several important influences on the drug’s pharmacological profile. (i) It is difficult to antagonise the acute effects of buprenorphine with pure antagonists once the drug is established on the receptors; (ii) the drug has a long duration of action; (iii) buprenorphine does not display the manifestations of physical dependence because the biochemical equilibria established during chronic dosing return to normal levels when dosing is stopped so slowly that the imbalances which are the cause of the abstinence syndrome, do not occur.

CLINICAL PHARMACOLOGY

The reinforcing effects of opioids in man were evaluated at the Addiction Research Centre (ARC), Lexington, KY, by measurement of the level of

![Diagram of graphs showing rates of offset of the inhibitory action of normorphine (a), pentazocine (b) and buprenorphine (c), respectively, in naive guinea-pig ileum myenteric plexus longitudinal muscle strips challenged with naloxone (NAL). Numbers refer to nM concentrations. Reproduced with permission from Schulz and Herz [24].]
opiate-like perception by human post-addicts. In these studies [28] identification of buprenorphine was primarily as an opiate though in the therapeutic dose range when compared with morphine (in analgesic equivalent doses in the same experiment), recognition was equivocal. Historical comparison with pentazocine [29] also suggested less clear cut opiate recognition for buprenorphine. In higher doses (0.8–2.0 mg) buprenorphine was more clearly recognised as opiate and this also applied on chronic dosing of a high dose of buprenorphine (8 mg/day) in the direct addiction test. At these high doses dysphoric effects which are characteristic of pentazocine and similar antagonist analgesics were not experienced with buprenorphine.

In the direct addiction study at ARC, a daily subcutaneous dose of 8 mg, reached gradually over 2 weeks, was administered for a further 6 weeks. Naloxone failed to precipitate abstinence in all five participating subjects. At the end of the study subjects were withdrawn from drug treatment under double-blind conditions with insignificant abstinence effects until 14 days later when a mild morphine-like abstinence syndrome was established for which drugs were requested for relief. The Himmelsbach abstinence score for the first 10 days of withdrawal was lower than for any drug of proven central analgesic activity studied at ARC. Confirmation of these results was obtained by Mello and Mendelson [31] who administered daily doses of buprenorphine rising to 8 mg over 14 days and maintained for 10 days to 10 addict volunteers and found no signs of abstinence on drug withdrawal. In this study subjects reported that buprenorphine had opiate-like effects but in contrast to the 'rush' associated with heroin, a generalised feeling of contentment was reported. The slow onset of action of buprenorphine could be a significant factor limiting its misuse.

Investigation of the potential of buprenorphine as a detoxification agent in opiate dependence has provided information about the drug's ability to substitute for opiates. In an ARC study when subjects maintained on about 40 mg/day of oral methadone were abruptly transferred to sublingual buprenorphine (2 mg) only a mild abstinence syndrome was encountered and this was largely confined to autonomic effects. When the methadone dose was gradually reduced concomitant with the buprenorphine administration, surprisingly somewhat more intense abstinence effects were experienced [25]. In a larger study in Hong Kong, buprenorphine (6–14 mg p.o.) precipitated strong abstinence effects in heroin addicts presenting for detoxification. In a group of eleven subjects stabilised on methadone (40 mg p.o./day), only three completed the 14-day detoxification procedure with oral buprenorphine. The rest dropped out as a result of abstinence effects (Hollinrake, pers. commun.).

CLINICAL EFFICACY AND SAFETY

In its therapeutic dosage forms (0.3 and 0.6 mg ampoules and 0.2 mg tablets) buprenorphine is an effective analgesic for the treatment of moderate
to severe pain [26]. It might be expected that as a partial agonist buprenorphine would have a ceiling to its analgesic action which in certain circumstances would make it less effective than morphine. However, in most clinical studies of analgesics the effect level at which drugs are being compared is only defined by the doses used of the standard drug. In the case of morphine, 20 mg is normally the upper dosage limit. Since buprenorphine’s ‘ceiling’ is not below this level, in clinical trials buprenorphine has never been found to be less effective than morphine. Thus buprenorphine is a viable substitute for the opiates in most clinical situations.

Though in the therapeutic dose range buprenorphine is associated with respiratory depression at a level equivalent to that of morphine, the dose-response curve must be very shallow or even be bell-shaped as in rats, since very high single doses (up to 7 mg i.v.) have been administered to non-tolerant patients without significant respiratory depression [27].

Buprenorphine is well absorbed by the sublingual route (0.4 mg = 10 mg i.m. morphine) whereas when swallowed its bioavailability is considerably lower (0.4 mg s.l. = 2 mg p.o. approx.). This confers even greater safety on the sublingual tablets in the situation of deliberate overdosage since a large number of tablets are much more likely to be swallowed than dissolved under the tongue. The sublingual dosage form is of particular value in the treatment of chronic pain where its benefits in terms of physical dependence are seen.

USE AND MISUSE OF BUPRENORPHINE

Buprenorphine is approved for sale in 45 countries; the injection product is on sale in 29 countries and the sublingual tablets in 16 countries. By the end of 1983 the cumulative number of units sold was approaching 70 million.

Misuse of buprenorphine has been reported in West Germany, New Zealand and Western Australia. This activity has involved opiate users who have turned to buprenorphine when their preferred drugs have been unavailable or too expensive or as a means of suppressing opiate withdrawal effects. Misusers do not appear to have come to harm from their use of buprenorphine. A minority of buprenorphine misusers may have become psychologically dependent on the drug but evidence for the establishment of significant tolerance or physical dependence in these subjects, is lacking. Anecdotal reports of the appearance of abstinence effects within a short time following the taking of only a few doses of buprenorphine have been received. These are most likely effects precipitated by buprenorphine and not attributable to buprenorphine dependence. The enhancement of abstinence when other opiates are taken as well as buprenorphine as outlined above in the ARC studies [25] makes the attribution to buprenorphine dependence even less justified.

CONCLUSION

Buprenorphine is a partial morphine-like agonist of limited reinforcing
efficacy and low toxicity with a unique freedom from acute abstinence effects following chronic administration. This profile prompted Martin [17] to observe 'although buprenorphine is a morphine-like drug, its relatively low ceiling of activity may make it not only a particularly safe analgesic but one which will produce a minimal and perhaps clinically insignificant degree of physical dependence'. More recently when the clinical utility of the drug had been better established, Martin [30] made the further comment 'It has only been with buprenorphine that an analgesic has been discovered which has a sufficient degree of agonist activity to produce a clinically desired effect, but not enough to produce a degree of physical dependence that would, in itself, give rise to drug seeking behaviour'.

REFERENCES