NARCOTIC ANALGESICS: “NUCLEAR MODIFIED” MORPHINE

I. Introduction: The “Synthetic Narcotic Analgesics”

More extensive structural modification of morphine has been carried out in an attempt to achieve more favorable separation of therapeutic (analgesia, antitussive) and adverse (respiratory depression, sedation, physical dependence) reactions. Continued SAR studies of nuclear modified opiates suggested that a minimum “structural” pattern (analgesiophore) exists in the relatively complex morphine structure that is primarily responsible for narcotic analgesia produced by this agent. The analgesiophore consists of an aromatic ring linked to a quaternary carbon which, in turn, is connected via a two carbon atom chain to a tertiary, basic amine. These studies led to the design and development of narcotic analgesics of simpler structure which are outlined below.

II. Morphinans

Morphinans are structurally derived from morphine by removal of the ether oxygen (ring E) and therefore elimination of the E-ring. The (-)-morphinan analogue derived from such a modification is levorphanol (Levo-Dromoran) which is a mu and kappa-3 receptor agonist. It is approximately 5-8 times more potent than morphine both as an analgesic and respiratory depressant, but produces less nausea and vomiting. Levophanol is more lipophilic than morphine and has a greater oral/parenteral potency ratio (2:1). It is available as a bitartrate salt which is administered orally and by injection (IM and SC) and has a duration of 3-6 hrs. It is cleared primarily by 3-O-glucuronidation similar to morphine.

The (+)-isomer of levophanol with a 3-methylether group is dextromethorphan. Dextromethorphan is inactive as an analgesic, but has antitussive potency equal to that of codeine.
Replacement of the N-methyl moiety in the morphinan series with an N-allyl or N-cycloalkyl groups results in partial agonist activity. Butorphanol tartrate (Stadol) is an agonist at $\sigma$ and $\kappa$-opiate receptors and a partial agonist/antagonist at $\mu$-receptors. As an analgesic (agonist) it is 5-times more potent as an analgesic than morphine with a similar onset and duration of action, a ceiling effect on the degree of respiratory depression occurs after about twice the usual therapeutic dose, has low abuse liability. As a $\mu$-antagonist this compound is about 6 times less potent than naloxone:

Butorphanol is available as the tartrate salt with is administered IM, SC and IV. It is metabolized by hydroxylation.

III. 5,9-Dimethylbenzomorphans

Benzomorphans such as metazocine shown below are structurally derived from morphine via cleavage of both ring C and E. Removal of these rings yields a benzomorphan ring system that has conformational flexibility (unlike the morphines and morphinans), thus different ring conformational extremes may exist. Also, the presence of methyl substituents at positions 5 and 9 in these compounds produces sites of asymmetry. Thus the benzomorphans can exist in different stereoisomeric and conformational forms (see next page). As noted earlier, the opiate receptors are capable of stereoselective ligand binding. Thus it is not surprising that different stereoisomeric forms of the benzomorphans differ in analgesic potency. In the case of the metazocine, the trans-5,9-diCH$_3$ stereoisomers (also termed beta isomers) are significantly more active as analgesics than the cis- (alpha) geometric isomers.

Overall, metazocine isomers are kappa agonists which are only about 1/6$^{th}$ the activity of morphine. Metazocine is available as HCl and tartrate salts which are orally active. The oral/parenteral potency ratio is 2:1. These compounds are metabolized 3-O-glucuronidation and hydroxylation of the side chain methyl groups.
Replacement of the N-methyl of metazocine with an N-allyl group yields pentazocine (Talwin). This compound is a relatively strong opiate agonist at kappa receptors and weak agonist/antagonist at mu receptors. It is most effective vs. moderate pain but tolerance and abuse potential do exist.

Pentazocine is available for oral administration and injectables (IM, SC). It’s oral bioavailability is relatively due due to extensive first pass metabolism by 3-O-glucuronidation and terminal methyl group oxidation; two different geometric isomers can form from methyl group oxidation. All of these metabolites are inactive.
IV. 4-Phenylpiperidines (4-PP)

The 4-phenylpiperidines can be regarded as analogues of morphine in which rings B, C and E have been removed as illustrated by the figure below and the example of meperidine:

Meperidine (Demerol) is the only 4-PP currently marketed in the U.S. It is an achiral analgesic that can exist in two different conformation extremes resulting from piperidine ring conformation inversion. In these conformations, the relative positions of the 4-substituents interconverts from axial to equatorial. It is believed that the conformation with the 4-phenyl group in the axial orientation in most stable and may be bound by opiate receptors:

Another class of 4-phenylpiperidines are the “prodines” these are analogues of meperidine in which the ester functionality has been “reversed” (not really significant here) and a methyl substituent added to the 3-position of the piperidine ring (significant). The additional methyl group creates chirality at both positions 3 and 4-stereochemical and thus provides an interesting experimental compound to study the relationship between opioid stereochemistry and opiate receptor binding:
Meperidine is a mu agonist but is 5-10 times less potent than morphine. It is no antitussive activity. Meperidine is available as the HCl salt for oral administration (tablets, syrup) and a solution for injection (IM). Meperidine has relatively high oral bioavailability (o/p ratio of 3:1) producing, at equi-effective doses, the same degree of analgesia, sedation and respiratory depression. Meperidine has a relatively short duration of action due to efficient inactivation by ester hydrolysis to meperidinic acid. A fraction of the dose is also metabolized by oxidative-N-dealkylation, leading to the formation of normeperidine which has been implicated in the CNS toxicity of meperidine. Meperidinic acid and normeperidine form a common normeperidinic acid which is conjugated and eliminated:

\[
\begin{align*}
\text{Meperidine} & \rightarrow \text{Meperidinic Acid (Inactive)} \\
& \rightarrow \text{Normeperidine (Less Active)}
\end{align*}
\]

Several merpidine-type analogues, or meperidine/methadone hybrid analogues including diphenoxylate (Lomotil) and Loperamide (Imodium) have been developed as antidiarrheal agents. These compounds have minimal analgesic activity, but retain the GI motility-inhibiting actions of the classic morphine-type drugs.
V. 4-Anilidopiperidine (4-AP) Derivatives

The 4-anilidopiperidines can be regarded as derivatives of the 4-phenylpiperidines in which a nitrogen atom has been inserted between the piperidine ring and the aromatic ring. Generally 4-anilidopiperidines are extremely potent narcotic analgesics (200 to 500 X morphine) with significant sedative properties. Thus they are used to aid the induction and maintenance of inhalation anesthesia and to supplement regional and spinal anesthesia.

The commercially available 4-anilidopiperidines include the parent or prototype, fentanyl (Sublimaze) and sufentanil (Sufenta), alfentanil (Alfenta) and remifentanil (discussed later). These compounds differ only in the nature of the piperdine N-arethylaryl substituent, and the nature of the “other” substituent at the 4-position. All of these compounds are primarily mu-agonists.

- Fentanyl is 25-80 times more potent than morphine with a shorter duration of action. Fentanyl is available as the citrate salt for injection (IM or IV) and transdermal patches. It is combined with droperidol (Innovar) and used to induce anesthesia.
- Sufentanil (Sufenta) is about 7-times more potent than fentanyl (about 800 times more potent than morphine) and has a slightly more rapid onset of action. It is available as
the citrate salt as a solution for injection (IV) and used to induce anesthesia and for postoperative analgesia.

- **Alfentanil (Alfenta)** is about as potent as fentanyl and has a shorter duration of action. It is available as the HCl salt for IV injection and used to induce anesthesia and for postoperative analgesia.

Due to a similar (isosteric) N-arylethyl fragment present in all of the 4-anilidopiperidines, these compounds are metabolized by a common pathway involving cytochrome-mediated N-dealkylation (see figure below). In fact, since alfentanil and sufentanil differ only in the nature of the aryl group in the N-arylethyl fragment, these two 4-anilidopiperidines yield the SAME OND metabolite. The OND metabolites formed from the 4-anilidopiperidines are inactive as analgesics. Alfentanil and sufentanil also contain a 4-methoxymethyl substituent which undergoes cytochrome-mediated oxidative O-demethylation (see below). The alcohol products formed from this reaction retain analgesic activity, but are oxidized to the corresponding acids which are inactive.

\[
\text{CH}_3\text{CH}_2\text{N}^+\text{Ar}X\quad 1. \text{Redistribution} \\
\quad \quad 2. \text{OND} \quad \text{(Cytp450)} \\
\text{CH}_3\text{CH}_2\text{N}^+\text{H} \quad \text{Further oxidative metabolism} \\
\text{CH}_3\text{CH}_2\text{N}^-\text{ArCH}_2\text{OH} \quad \text{OOD (X=CH}_2\text{OCH}_3) \\
\text{CH}_3\text{CH}_2\text{N}^-\text{HCOOH} \quad \text{CH}_3\text{CH}_2\text{N}^-\text{H}
\]

Remifentanil is a 4-anilidopiperidine designed as a soft drug. It is similar to the other members of this series in its pharmacologic profile and is 20-50 times more potent than alfentanil. Remifentanil differs from the other 4-anilidopiperidines in that it is designed as a "soft drug" – a compound that is designed to be metabolized rapidly so it has a relatively short duration of action:
VI. Aminotetralines: Dezocine

Dezocine (Dalgan), a synthetic bridged aminotetralin is a structurally-novel partial (mixed) opioid agonist/antagonist. This is the only primary amine compound to display opioid activity! Dezocine’s profile of opiate receptor subtype affinity is similar to that of morphine with partial agonist activity at \( \mu \)-receptors (RP=1). The incremental analgesia observed with successive doses of dezocine in addition to somnolence elicited by the drug suggest activity at opiate \( \kappa \)-receptors. Unlike pentazocine, butorphanol and nalbuphine, dezocine does not possess high affinity for \( \sigma \)receptors. The compound is 8.6 times more potent than pentazocine as a respiratory depressant, however a ceiling respiratory effect occurs for this agent at 0.30 mg/kg.

Dezocine is available as a a solution for IM, SC or IV injection. It is cleared by glucuronidation and reductive metabolism (?).

VII. Arylcyclohexanolamines: Tramadol

Analogue of codeine in which rings B, D and E have been removed. This structure contains two chiral centers (positions 3 and 4 of the cyclohexane ring), thus there are four potential stereoisomers – enantiomeric cis and trans isomers (see below). The racemic cis isomers are active and make up the commercial product.
Tramadol (Ultram) is a mu agonist that is substantially less potent than morphine as an analgesic (more than 100 fold less active). This product also has peripheral analgesic actions. Tramadol has high oral activity and is metabolized by cytochrome-mediated oxidative-O-demethylation to the corresponding 3-phenol which is more active than the parent drug. The phenol is glucuronidated and eliminated. A fraction of the tramadol dose is also metabolized by cytochrome-mediated oxidative-N-demethylation to less active metabolites.

**TRAMADOL STEREOISOMERS**

**cis isomers (active): In commerical product**

**trans isomers (less active): Not in commerical product**

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VIII. Diphenylpropylamines: Methadone, Levomethadyl Acetate and Propoxyphene

This structural class of narcotic analgesics is essentially an acyclic version of the 4-phenylpiperidines. Methadone is a diphenylpropylamines with an additional propanone (ketone) side chain. Levo-α-acetylmethadol (LAAM) is a methadone analogues in which the ketone has been reduced to an alcohol and that alcohol group esterified as an acetate ester.

Methadone (Dolophine, Methadon) is chiral (carbon alpha to nitrogen) and is marketed as a racemate. The (-)-isomer is the active analgesic isomer. Methadone is very similar to morphine in its pharmacologic (μ agonist with RP = 1) and toxicologic profile except that methadone is highly effective after oral administration and has a much longer duration of action (19 hours). The extended and variable duration of action (15-40 hours) results in part from the formation of a number of active metabolites as shown below. Methadone is marketed as the HCl salt for oral administration. Methadone is commonly used for maintenance therapy of narcotic addicts.

Levo-α-acetylmethadol (LAAM) is similar in structure, pharmacology and pharmacokinetic properties to methadone. LAAM is approved to treat heroin withdrawal. Note that levo-α-acetylmethadol and methadone are “metabolically related” giving rise to several common, active analgesic metabolites. As a result LAAM has a relatively slow onset and very long duration of action (72-96 hours). The nor-LAAM and dinor-LAAM metabolites shown below are more potent than the parent compound and achieve higher plasma levels than the parent compound during prolonged therapy.
Metabolism of Methadone and LAAM

Methadone

\[
\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{CYP450}}\]

Normethadone

\[
\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{Spontaneous Chemical}}\]

Pyrrolidine

\[
\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{CYP450}}\]

α-Methadol (Active)

\[
\text{CH}_3\text{OCH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{Esterases}}\]

α-Normethadol (Active)

\[
\text{CH}_3\text{OCH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{CYP450}}\]

α-Dinormethadol (Active)

\[
\text{CH}_3\text{OCH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{Esterases}}\]

LAAM

\[
\text{CH}_3\text{OCH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{CYP450}}\]

nor-LAAM (Active)

\[
\text{CH}_3\text{OCH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{CH}_3\text{NCH}_3\text{CH}_3\text{CH}_3\text{OCH}_3\]

\[\xrightarrow{\text{CYP450}}\]

Dinor-LAAM (Active)
Propoxyphene (Darvon, Dolene) also is a diphenylpropylamine analgesic. Propoxyphene is marketed as a racemic mixture and the (+)-isomer is active as a mu agonist. It is nearly ten-times less active than morphine as an analgesic and is somewhat effective in alleviating mild to moderate pain. This compound reportedly has less abusive potential than codeine. The (-)-isomer has antitussive activity. 

Propoxyphene is marketed as the HCl and napsylate salt (Darvon-N). The napsylate is available as tablets and an oral suspension. These products have higher oral bioavailability than morphine.

Propoxyphene is metabolized by cytochrome-mediated oxidative-N-demethylation to norpropoxyphene which is substantially less active. Norpropoxyphene may undergo further OND to yield Dinorpropoxyphene and cyclic-dinorpropoxyphene. Propoxyphene and its nor- and dinor-metabolites also undergo esterase hydrolysis to yield the carbinol metabolites. Propoxyphene and its nor-metabolites also undergo aromatic hydroxylation to yield the phenolic metabolites: All of these metabolites are reportedly less active than the parent drug.
Summary of the opiate receptor binding profiles of the opioid drugs

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<th>Opioid</th>
<th>µ</th>
<th>δ</th>
<th>κ</th>
<th>σ</th>
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<tr>
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<td>+++</td>
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<tr>
<td>Met-enkephalin</td>
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<td>+++</td>
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<tr>
<td>Morphine</td>
<td>+++</td>
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<tr>
<td>Codeine</td>
<td>+</td>
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<tr>
<td>Etorphine</td>
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<td>Fentanyl</td>
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<td>(++)</td>
<td>(++)</td>
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</tr>
<tr>
<td>Buprenorphine</td>
<td>(++)</td>
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Antagonists

| Naloxone         | ---  | --  | -- |   |
| Naltrexone       | ---  | --  | -- |   |

+ agonist, - antagonist, (+) partial agonist