Recent advances and developments in the clinical use of i.v. opioids during the peroperative period

J. W. Sear

The provision of general anaesthesia requires the administration of drugs to suppress movement in response to noxious stimuli and responses to autonomic stimulation of the sympathetic and parasympathetic nervous systems, to abolish awareness, and to relieve pain. Pain relief can be achieved by use of nitrous oxide as part of a balanced anaesthetic; by opioids or related drugs given intravenously or systematically; by other drugs having analgesic properties (for example, phencyclidines such as ketamine, or the NSAIDs); or by local anaesthetic agents, given topically by local infiltration to provide nerve or plexus blockade, or by the spinal route. In this review I shall consider the use of opioid drugs as part of balanced or other anaesthetic techniques for anaesthesia.

The analgesic properties of morphine have been known since they were described by Theophrastus in the third century BC, but there is a continuing quest for newer and pharmacologically purer drugs that bring about analgesia without the unwanted other effects of the opium alkaloids. The first such synthetic agent was pethidine, produced in 1938; its use as part of a balanced technique using nitrous oxide was described by Neff and colleagues. In 1958 Bailey and colleagues used pethidine with oxygen for cardiac surgery. This led in turn to reports of the cardiovascular stability observed when large doses of morphine (0.5–1.0 mg kg⁻¹) were given to patients with compromised cardiovascular function. However, the technique was not without its problems, namely intraoperative recall, failure to prevent intraoperative hypertension, histamine-related hypotension and increased perioperative fluid requirements. In an attempt to remedy these side effects, some clinicians used even larger doses of morphine (up to 10 mg kg⁻¹), although this was found to be associated with greater haemodynamic instability. Other side-effects included the potential for addiction and pronounced respiratory depression.

In the course of the evaluation of alternative drugs with a greater analgesic selectivity, nalorphine was synthesized. Nalorphine not only reversed the respiratory depressant effects of morphine but also had intrinsic analgesic properties. This led to the development of other drugs showing mixed agonist and antagonist activities (such as pentazocine, butorphanol and buprenorphine), and the concept that there was more than one type of opiate receptor.

The introduction of fentanyl and development of the various newer congeners (especially alfentanil and sufentanil, and more recently remifentanil) has allowed the clinician to use drugs with analgesic and other properties similar to those of morphine and pethidine, but with greater potency, inactive metabolites and fewer side effects — particularly those relating to histamine release.

Newer synthetic opioids in clinical practice

FENTANYL

Fentanyl, the first of the present generation of potent anilino-piperidine opioids, was introduced into clinical practice in the mid-1960s. It was shown to be 100–300 times as potent as morphine, with a high therapeutic index, and fewer adverse side effects. In combination with nitrous oxide or with major tranquillizers such as droperidol, fentanyl produced analgesia, amnesia, an absence of obvious motor activity, depression of autonomic reflexes and, importantly, cardiovascular stability.

The opioid was often administered as an initial bolus dose of 0.2–0.3 mg with supplements of 0.1 mg or by a continuous infusion. One problem with fentanyl was the wide inter-individual variability, as typified in the paper of Reilly and colleagues, who described a wide range of variability in disposition (when expressed as plasma concentration–time data) within seven different sets of parameters.

In the 1990s, the optimal strategy for dosing with fentanyl is probably that of “balanced anaesthesia”, where fentanyl is supplemented by isoflurane or another volatile agent. To provide analgesia, plasma drug concentrations need to be around 1–2 ng ml⁻¹; this can best be achieved using a loading dose of 2–8 μg kg⁻¹ and an infusion thereafter of 0.5–3.0 μg kg⁻¹ h⁻¹.

However, there is a problem with infusing fentanyl for intraoperative analgesia — this highly lipid-soluble drug is significantly liable to accumulate in lipophilic peripheral tissues, with a resulting marked increase in the “context sensitive half-time” (see later) (fig. 1).

Keywords: kidney, disease; liver, disease; pharmacodynamics; anaesthetics opioid; pharmacokinetics, anaesthetics opioids; pharmacology, anaesthetics opioids
ALFENTANIL

Alfentanil shows about one-fifth the potency of fentanyl; it is shorter acting and has a faster onset-to-peak effect. There are many reports of the use of alfentanil to supplement nitrous oxide for surgery. However, few studies have recruited sufficient participants to demonstrate the full side effects profile of the opioid, whether used alone or in combination with an hypnotic or volatile agent.

In a multicentre study from Canada, a continuous variable-rate infusion of alfentanil (0.5–1.5 \( \mu \text{g kg}^{-1} \text{min}^{-1} \)) was used to supplement 67% nitrous oxide and isoflurane. The duration of anaesthesia averaged 117 min, with the infusion being stopped 10–15 min before the expected end of surgery. Postoperative recovery times were measured from cessation of nitrous oxide and isoflurane to opening eyes on command (6 min), response to verbal commands (8 min), and full alertness (22 min). However this apparent prompt and complete recovery from the alfentanil–isoflurane combination was at the cost of perioperative side effects: hypotension was seen in 26.2%, hypertension in 20.6%, bradycardia in 14.9% and tachycardia in 12.1%. Other side effects included muscular rigidity (8.4%), nausea (13.1%) and vomiting (4.7%). However, many of these effects were considered not to be attributable to the alfentanil; and overall satisfaction with the conduct of anaesthesia was more than 98%.

SUFENTANIL

In contrast to fentanyl, sufentanil is 7–10 times more potent than the parent drug. It has a higher affinity for stereospecific receptor-binding sites, and shows minimal binding to nonspecific sites. There is, however, a slower dissociation rate from the \( \mu \) receptor.

When used in balanced anaesthesia or as a sole agent sufentanil is more effective than fentanyl, for reasons that are somewhat unclear. The agents have similar onset times but the duration of sufentanil is shorter, especially when the drug is given by multiple dosing or continuous infusion. Its elimination half-life (140–200 min) is shorter than that of fentanyl (150–400 min).

When given in doses of 10–25 \( \mu \text{g kg}^{-1} \) as a sole agent for cardiac and major vascular anaesthesia, sufentanil was associated with evidence of improved outcome. However, Philbin and colleagues were unable to define plasma concentrations associated with no response to intubation and sternotomy.

There is some suggestion that in cardiac surgical patients sufentanil provides better intraoperative stability than fentanyl, in terms of decreased hypertension and tachycardia, and hence reduced myocardial oxygen consumption, and shorter postoperative respiratory depression.

REMTIFENTANIL

At the time of writing (October 1997) there are few published data on the clinical use of remifentanil in comparative studies with other analgesic drugs. However, in a recently published comparison with alfentanil (1.0 \( \mu \text{g kg}^{-1} \text{min}^{-1} \)), infusions of remifentanil (0.5 \( \mu \text{g kg}^{-1} \text{min}^{-1} \)) were given to supplement 67% nitrous oxide and 0.4% isoflurane in patients undergoing lower abdominal surgery. The infusion rates were halved after intubation, and bolus doses given or the infusion rates changed if there were positive responses to surgical stimuli.

In the remifentanil group, fewer patients responded to intubation and incision, and during surgery. At the end of the operation, recovery to extubation was marginally faster in the remifentanil group, but there were no differences in times to onset of spontaneous ventilation, response to verbal command and discharge from the recovery room. Comparing the side effect profiles of the two drugs, the overall incidence was similar in the two groups; but the remifentanil group showed a higher intraoperative incidence of bradycardia and hypotension. The remifentanil infusion was continued after operation in that arm of the study, but was associated with reports of postoperative apnoea and muscular rigidity. It is difficult to draw overall conclusions from the study, because it appears that non-equipotent doses of the two drugs may have been used during operation and the postoperative infusion of remifentanil would seem to require intensive supervision of the patients on a one-to-one basis to detect apnoea and respiratory depression, which may be impractical with the routine staffing levels of most recovery units.

Two other areas of interest relate to use of the opioid during neurosurgical and cardiac anaesthesia. Guy and colleagues have compared remifentanil and fentanyl during anaesthesia in patients undergoing supratentorial craniotomy. The opioids were given by infusion to supplement 67% nitrous oxide (1 and 2 \( \mu \text{g kg}^{-1} \text{min}^{-1} \), reducing to 0.03 and 0.2 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) respectively). Additional boluses of 1 and 2 \( \mu \text{g kg}^{-1} \) of remifentanil and fentanyl were given, or stepwise increases made in the infusion rates, to control increases in systolic arterial pressure or heart rate; if these increases were not controlled by infusions of 0.06 and 0.4 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) respectively, isoflurane was added.

Remifentanil had the greater effect on the haemodynamic response to intubation, and more isoflurane was used in the patients receiving fentanyl. Recovery at the end of anaesthesia was similar in the two groups, as were the incidences of nausea and vomiting. Again, there was no evidence from preliminary studies of the equipotency of these two regimens.
When used for cardiac anaesthesia, the short context-sensitive time of remifentanil was considered a potential advantage in the “fast tracking” of patients undergoing coronary artery bypass grafting (CABG). In a retrospective comparison with their routine fentanyl–inhalational technique, Bacon and colleagues found no differences between treatments in the haemodynamic responses to surgery.7 Remifentanil has been shown to attenuate the increases in catecholamines during CABC.4 While Bacon and colleagues found that their patients receiving remifentanil could be extubated soon after surgery (70% within 3–5 h), this has not been the experience of Duthie and colleagues.35

High doses of opioid agonists (alone or in combination with hypnotics or volatile agents) will obtund or abolish intraoperative neuroendocrine responses to pelvic and lower abdominal surgery, but not to upper abdominal, thoracic and cardiac surgery. The three main anilino-piperidine opioids (fentanyl, alfentanil and sufentanil) have all been associated with the occurrence of postoperative respiratory depression.111 Several reasons for this have been suggested, including enterogastric recirculation of drug leading to secondary concentration peaks; alterations in body pH and hence increases in the percentage of free opioid in the plasma; and the presence of abnormal drug metabolizers that cause significant reduction of drug clearance.9 10 114 In the case of alfentanil, the relevance of genetic variability in drug handling has recently become significant (see later).

One of the main reasons for the development of “opioid-alone anaesthesia” was the cardiovascular stability and avoidance of potentially significant drug–drug interactions (for example, the profound stability and avoidance of potentially significant “opioid-alone anaesthesia” was the cardiovascular stability and avoidance of potentially significant interaction of plasma drug concentration and clinical response. However, several authors have studied the concentration–effect relationship for postoperative analgesia. Graves and colleagues defined a minimum effective concentration (MEC) during patient-controlled analgesia (PCA) of 20–40 ng ml−1,45 which was broadly in agreement with the data of Dahlstrom and colleagues, and Gourlay and colleagues.29 45 However it is only recently that the contribution of the 6-glucuronide of morphine to “total analgesic effect” has been fully realized, and hence estimates of plasma morphine concentrations as indices of analgesia are probably an over-simplification.

We examined “time to first analgesia” after single i.v. doses of morphine 10 mg to supplement volatile–nitrous oxide anaesthesia for general surgery in healthy, benzodiazepine-premedicated patients, and our data support this value for MEC, with plasma morphine concentrations of 50–150 nmol l−1.112

In the case of pethidine administered as part of balanced anaesthesia there are few data, and the active metabolite norpethidine is a complicating factor. Austin and colleagues found a relationship between analgesia and pethidine concentrations of the order of 0.5–0.7 μg ml−1 for patients undergoing general surgery with balanced anaesthesia.6 These tally with the findings of Tamsen and colleagues, who showed that mean postoperative plasma pethidine concentration during PCA was 551 ng ml−1 and ranged between 130 and 900 ng ml−1.124 There is the added complication for pethidine of a very steep concentration–effect relationship, such that concentration differences of as little as 0.05 μg ml−1 may represent the difference between no analgesia and complete pain suppression.

After i.v. dosing about 65% of pethidine is taken up by the lungs, although it is released back into the circulation within 1–2 min.103 Plasma protein binding of pethidine is higher than that of morphine (with 70% bound to plasma proteins, mainly α1-acid glycoprotein, and only a small percentage to albumen). Pethidine is mostly broken down by N-demethylation and hydrolysis to norpethidine, pethidinic acid and norpethidinic acid. The former has some opioid effect, and undergoes renal excretion — so that its effect is more pronounced in patients with renal impairment. Norpethidine also has twice the liability of the parent drug to cause seizures when accumulated in renal failure; this effect is not reversed by naloxone.51

ANILINO-PIPERIDINES

The disposition kinetics of fentanyl, alfentanil and sufentanil have been reviewed elsewhere.16 17 21 41 50 55 56 109 However, several important generalizations on their kinetics are relevant to clinical practice. Sufentanil and fentanyl show no evidence of dose-dependent kinetics,31 although there is a suggestion that such kinetics may occur with alfentanil.102 All of the drugs are weak bases, and their ionization is therefore affected by the Henderson–Hasselbach equation.

Fentanyl

Fentanyl shows significant binding to plasma proteins (about 84%), and a high first-pass uptake by the lungs (about 75%), from which it is released in a
bimodal fashion.103 123 Fentanyl binds to both albumen (about 50%) and to α- and β-globulins. Any change in drug binding caused by disease or other interaction may lead to significant alterations in drug dynamics, particularly with respect to respiratory activity.

If we assume that the EEG responds to the concentrations of fentanyl in the brain, these have been shown by Scott and colleagues to parallel those seen in the plasma but with a lag time of about 5 min.107 The marked hysteresis is accounted for by the drug’s lipophilicity and uptake into non-receptor fatty tissues of the central nervous system before binding to its main sites of action. Because of this marked delay in effect, fentanyl should ideally be given about 5 min before the application of a noxious stimulus, or else given in a dose larger than needed so that it saturates the brain and other storage-binding sites. The large volume of distribution of fentanyl also results in considerable variation of plasma concentrations for a given dose,20 as well as the occurrence of secondary peaks in the concentration–time profile of the opioid at times of altered peripheral blood flow (that is, during recovery from anaesthesia and surgery).

**Alfentanil**

Alfentanil is less lipid-soluble than fentanyl (heptane: water partition coefficients 2.5 vs 9.0), and shows little non-receptor binding in brain tissue. Plasma protein binding of alfentanil is mainly to α1-AGP and shows a very limited non-specific brain binding. Sufentanil has a pKa of 8.0, and therefore only a small fraction (20–60%) is ionized. At physiological pH, most of the drug is in an un-ionized form because of its low pKa (6.5). Alfentanil has a hepatic extraction ratio of 0.3–0.5, and is mainly metabolized by the cytochrome P450 isoform IIIA3/4, the most abundantly expressed of the hepatic P450 isoenzymes (20–60%).52 The role of the isoenzymes has been further evaluated in vivo by the same authors, who then modelled the data to see the influence of isoform induction on the context-sensitive half-time of the opioid (fig. 2).21 The simulations clearly explain part of the variability in the kinetics (and dynamics) of this opioid previously defined as “predictable and short-acting”.

Alfentanil has a faster equilibration of the drug concentration between blood and brain (biophase) than is seen with the other fentanyl congeners (t1/2 k0: 0.9 min compared with 4.7 and 5.8 min for fentanyl and sufentanil)106 107 with the exception of remifentanil. Alfentanil dosing is therefore more easily titratable to effect. Studies by Ausems and colleagues and Lemmens and colleagues66 69 have modelled the concentration–dynamic effect relationship when alfentanil by infusion has been given to supplement nitrous oxide. For patients undergoing general surgical procedures, the Cp50 plasma concentrations of alfentanil to supplement nitrous oxide–oxygen anaesthesia are shown in table 1. Plasma alfentanil concentrations of about 2000 ng ml−1 provide adequate anaesthesia for sternotomy during cardiac surgery.56

**Sufentanil**

Because of the high potency of sufentanil, and poor sensitivity of the radioimmunosorbent assay for measurement of plasma and tissue drug concentrations, early kinetic studies of sufentanil were conducted in patients receiving large doses of the drug for cardiothoracic anaesthesia.14 There are few reliable data sets describing sufentanil’s use in balanced anaesthesia,109 where the kinetics are clearly influenced by the duration of sampling. Gepts and Shafer have examined the drug’s disposition after i.v. doses of 250–1500 μg given over 10–20 min, with arterial blood sampling for drug concentrations to 48 h.41 They defined the kinetics of sufentanil as follows: clearance = 0.92 ± 0.1 min−1; apparent volumes of distribution, V1 = 14.3 l, V2 = 261.6 l, Vss = 339 l; elimination half-life = 769 min. The calculated hepatic extraction ratio for sufentanil was 0.8. Plasma protein binding of sufentanil is in the range 90–92%.51 52

**Remifentanil**

Remifentanil is a new opioid that undergoes widespread extrahepatic and hepatic breakdown by tissue and blood non-specific esterases, and therefore has a rapid clearance and short duration of effect.36 41 The major metabolite of remifentanil is also a pure

![Figure 2](https://example.com/figure2.png)
α-opioid agonist, but has a potency of only about 1/4600 of the parent compound. This metabolite (GR90291) has been shown by Hoke and colleagues to have a half-life of 19 min in dogs (compared with 5.6 min for remifentanil and 20 min for alfentanil).\textsuperscript{52} Using the index of 50% maximum delta EEG activity response, and the 95% spectral edge, remifentanil was 4213–4637 times as potent as the metabolite, although the blood–brain equilibration of the metabolite was significantly faster (0.4 min vs 2.3 and 5.2 min respectively).

Remifentanil and fentanyl differ mainly in their kinetics, such that remifentanil can be switched ‘on- and-off’ very rapidly. This facilitates titration of dose to effect, allowing ready control of responses to noxious and painful stimuli. In excess, remifentanil is associated with the rapid onset of hypotension, bradycardia, apnoea and muscle rigidity; the drug is therefore best given as a short infusion (over 1 min) rather than as a bolus dose, and patients should be pre-treated with anticholinergics if remifentanil is to be used.

Because of its rapid elimination half-life (3–10 min) and context-sensitive half time of 5–10 min even after prolonged infusion, the anaesthetist can give remifentanil at the maximally beneficial rate (for example the ED\textsubscript{50} rate) without the problems of a prolonged recovery when drug administration ceases.

In assessing the potency of these opioids, several surrogate endpoints have been adopted, such as the drug concentration needed to bring about a half-maximal slowing of the EEG,\textsuperscript{44} 106–108 or the concentration needed to reduce the MAC of a volatile agent.\textsuperscript{10} 44 67 77 131 In the case of remifentanil, the drug is a little less potent than fentanyl, and has an onset similar to that of alfentanil. For the two endpoints described, the potencies can be summarized as follows:

For EEG slowing, sufentanil is 12 times as potent as fentanyl, while fentanyl and remifentanil are 75 and 16 times as potent as alfentanil.

When assessed on the basis of MAC reduction, the relative potencies of sufentanil, fentanyl, remifentanil and alfentanil are 1:10:10:80.

### Table 1 Concentrations of alfentanil used to supplement nitrous oxide–oxygen anaesthesia in patients undergoing general surgical procedures. (Data from references 4, 5, 68 and 69)

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>(C_{50}) Concentration (ng ml(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation</td>
<td>475 (28)</td>
</tr>
<tr>
<td>Skin incision</td>
<td>279 (20)</td>
</tr>
<tr>
<td>Skin closure</td>
<td>150 (23)</td>
</tr>
<tr>
<td>Breast surgery</td>
<td>270 (63)</td>
</tr>
<tr>
<td>Lower abdominal surgery</td>
<td>309 (44)</td>
</tr>
<tr>
<td>Upper abdominal surgery</td>
<td>412 (135)</td>
</tr>
</tbody>
</table>

**Rationales for the use of i.v. analgesic drugs**

**BALANCED ANAESTHESIA**

**Induction of anaesthesia**

Opioid drugs are commonly used as part of an induction sequence to provide a smooth onset to anaesthesia and, more importantly, to obtund the haemodynamic responses to laryngoscopy and intubation.

To achieve onset of anaesthesia with alfentanil alone, McDonnell and colleagues found the ED\textsubscript{50} dose for loss of verbal command to be 111 \(\mu\)g kg\(^{-1}\).\textsuperscript{67} Other opioids (sufentanil, fentanyl and remifentanil) do not appear to offer these same properties of loss of consciousness without the significant side effects of excessive involuntary movements and truncal rigidity.

More recent interest has focused on the combination of opioids with hypnotic drugs or benzodiazepines to provide induction of anaesthesia\textsuperscript{80 116 119 126}, and the residual analgesia persisting after the induction sequence often prevents the need for further analgesic supplementation, especially when sufentanil or fentanyl have been used. Vinik and colleagues have examined the hypnotic effects of propofol, midazolam and alfentanil in dual and triple combinations. Alfentanil acted synergistically with both midazolam and propofol, but the triple combination showed no greater efficacy than midazolam–alfentanil alone.\textsuperscript{127}

**MAINTENANCE OF ANAESTHESIA**

Administration of opioids to provide intraoperative and often postoperative analgesia may also obtund the haemodynamic responses to intraoperative noxious stimuli. The co-administration of opioids with volatile agents during balanced anaesthesia will also cause significant reductions in the MAC of the volatile agents\textsuperscript{44 67 77 131} and intraoperative volatile requirements. However at very high opioid concentrations, there is a “ceiling effect” with no further reduction in the end-tidal volatile concentration (fig. 3). In the case of fentanyl, the steepest reduction in the isoflurane requirement occurs within the analgesic concentration range (0.5–2 ng ml\(^{-1}\)).\textsuperscript{77}

Because of the longer durations of action of boluses of fentanyl and sufentanil, dosing to supplement nitrous oxide anaesthesia can be satisfactorily achieved with a loading dose followed by bolus increments.\textsuperscript{44}\textsuperscript{106} For alfentanil and remifentanil, continuous infusion is the optimum strategy.\textsuperscript{32 45} The rapid response of the patient to changes in plasma concentration of alfentanil or remifentanil (because of their short blood–brain equilibration half-times) allows easy titration of drug dose to clinical response.

Vuyk and colleagues have similarly evaluated an opioid-hypnotic interaction in patients undergoing lower abdominal surgery and receiving an infusion of alfentanil.\textsuperscript{129} If the alfentanil infusion is maintained into the postoperative period, computer modelling has defined the optimum combination of propofol–alfentanil to achieve analgesia and the most rapid possible recovery in 50% of patients.\textsuperscript{130}

**TOTAL INTRAVENOUS ANAESTHESIA**

**Maintenance of anaesthesia**

During total intravenous anaesthesia (TIVA), the required opioid doses and their associated plasma concentrations may vary from those needed during balanced anaesthesia, although TIVA techniques are often used for cardiac and other prolonged surgical procedures where postoperative ventilation is to be carried on.

When an opioid and a hypnotic agent are used to
provide total intravenous anaesthesia, the drugs interact to potentiate one another. Opioids have been shown by Vinik and colleagues to potentiate the hypnotic effects of the benzodiazepines; and in a separate study the interaction of propofol, alfentanil and midazolam were compared in 130 patients who had received no premedication. However, most of these studies were conducted using single i.v. doses of the various drugs. What happens when infusions of different drugs are administered simultaneously? When midazolam or propofol was used to provide total intravenous anaesthesia, Vuyk and colleagues found that, when alfentanil was given by variable-rate infusion to patients receiving fixed doses of midazolam or propofol, total dose requirements of alfentanil were similar. However recovery to various indices was faster after propofol–alfentanil.

In subsequent evaluations of the propofol–opioid technique, the groups from Leiden and Duke Universities have compared the dose requirements of the two groups of drugs when used to provide anaesthesia. The effect-site concentrations of three commonly used opioids (fentanyl, alfentanil and sufentanil) have shown the anaesthetist how to make an appropriate and rational choice of the correct opioid for surgery of different durations and associated with differing types of noxious stimuli.

For example, because of alfentanil’s rapid blood–brain equilibration time and short elimination half-life, bolus dosing is clearly the best when the aim is to obtund acute noxious stimuli. But what if the stimulus lasts longer? For brief-duration infusions (<30 min), there is little to choose between alfentanil, fentanyl and sufentanil in terms of the speed of offset (although the onset of effect of the latter two is slower than that of alfentanil). For long infusions (>120 min), alfentanil or sufentanil produce a faster recovery profile than fentanyl. For surgery lasting longer than 240 min, infusions of alfentanil are the preferred option if recovery depends on an 80% decrease in the maintenance opioid concentration, although there is little difference between alfentanil and sufentanil if only a 50% decline is required.

A further elaboration of the concept can be found in the data of Youngs and Shafer, who model the effects of varying infusion durations on not only the 50% decline in plasma drug concentration but also on the 20% and 80% declines (what are termed the “20%, 50% and 80% decrement times”). As the effect site (biophase) concentration is always related to the plasma concentration, the latter is a good descriptor of drug effect except after bolus doses or very short infusions.

**Influence of disease on the handling of opioids in man**

**EFFECTS OF LIVER DISEASE**

Because the liver is the main site of opioid metabolism, alterations in drug clearance may be expected in patients with hepatic dysfunction. However, several separate factors interplay one with another, including liver blood flow, liver microsomal enzyme activity, and the binding of drugs to protein and tissue. The increased free fraction observed in liver dysfunction may therefore counter-balance the decrease in mixed-function oxygenase activity.

In patients with cirrhosis, handling of drugs is usually affected because the marked fibrosis and nodular regeneration of the liver cause circulatory changes, such as portosystemic intra- and extra-hepatic shunting; increased plasma volume; increased cardiac output; peripheral pooling of blood; and hypoalbuminaemia. Acute viral hepatitis and alcoholic liver disease predominantly affect the pericentral regions of the hepatic lobules, and are therefore more likely to be associated with impairment of oxidative metabolism. Chronic active hepatitis (CAH) and primary biliary cirrhosis (PBC) affect mainly the perportal regions, and have little effect on drug metabolism. In a study of the handling of alfentanil during anaesthesia in patients with a variety of alcoholic and non-alcoholic liver diseases, we showed differences in drug clearance between control patients, and patients with alcohol-related and non alcohol-related liver disease.

**Figure 3** The interaction between fentanyl and isoflurane. The solid line (MAC) represents the concentration of the two drugs that will prevent movement at skin incision in 50% of patients. Adapted with permission from McEwen and colleagues.
Morphine

Because of the protected locale of those enzymes responsible for glucuronide conjugation, the kinetics of morphine remain unaltered until liver disease reaches the end stage. Approximately 10% of morphine conjugation occurs extra-hepatically in the gastrointestinal tissues and kidney, and in liver disease this can increase to 30%. In severe liver disease, morphine clearance is reduced by 50%, with a doubling of the elimination half-life.28 39 40 Similarly the bioavailability of orally administered opioids increases.81 90 96

In patients undergoing liver transplantation, Bodenham and colleagues showed that if a single bolus of morphine 10 mg was given i.v. at the start of the anhepatic phase of the surgery, there was still a rapid decline in plasma morphine levels, suggesting that metabolism might occur during this period.11 However, during the same period, plasma morphine 3-glucuronide and 6-glucuronide concentrations remained low, although there was a detectable urinary concentration of both metabolites. No normorphine was detectable. It seems likely that the reduced concentration of the parent drug may represent redistribution, as well as possible dilution by infused fluids. Another mechanism might be the uptake of morphine by the lung and other tissues.

Roerig and colleagues, Persson and colleagues, and Ratcliffe all report similar data.93 99 103 The first two groups observed probably non-significant uptake and no metabolism of morphine (of the order of 0–7%). After a single i.v. dose of morphine coupled with ICG, and collecting the arterial outflow until the peak in ICG was observed, thus avoiding possible contamination through recirculation, Ratcliffe detected no morphine metabolites; but the short sampling period may not have allowed for uptake, metabolism and subsequent release into the pulmonary venous circulation.99 Overall it seems unlikely that the lung is involved to any great extent in morphine disposition.

Pethidine

In patients with cirrhotic liver disease, the disposition of pethidine shows reduced drug clearance and increased elimination half life,44 96 but there are no published data looking at the effects of these kinetic changes on the dynamics of pethidine.

In contrast to morphine, there is evidence of significant pulmonary clearance of pethidine. Kramer and colleagues measured lung clearance to account for 46% total clearance in the dog,65 and this has been supported by values of more than 90% for peak extraction and 65% retention after a single dose before surgery.103 During a two-stage infusion regimen for postoperative pain relief, there was also significant pulmonary uptake, expressed as the venous-to-arterial concentration difference,91 but no evidence of overall clearance (as measured by metabolite formation). In the absence of liver function, it seems the lung cannot undertake the hepatic role of biotransformation of these two opioids.

Fentanyl and its congeners

The effects of liver disease on the handling of the anilino-piperidine opioids is complex. In patients with compensated hepatic cirrhosis undergoing surgery, Haberer and colleagues found no change in fentanyl kinetics.50 However, in patients with severe liver dysfunction undergoing abdominal aortic aneurysmectomy, the elimination half-life of both fentanyl and sufentanil was prolonged.55 56

In our comparative study in patients with alcoholic and non-alcoholic liver disease, plasma clearance was lower in non-alcoholic patients than in either alcoholic patients or healthy controls.17 In all three groups, there was considerable intersubject variability; distribution was bimodal in the non-alcoholic group, in whom there was also a smaller apparent volume of distribution at steady state. The mean residence time was, however, prolonged in the alcoholic group, where plasma protein binding was also decreased compared with controls (84.9% vs 89.3%). This was probably attributable to a lower plasma α1-acid glycoprotein concentration.

There are few data on the dynamic consequences of liver disease on opioid requirements during anaesthesia. However, in patients undergoing breast surgery, Lemmens and colleagues have shown that the Cp50 concentration for alfentanil was greater in those with an increased alcohol intake compared with controls.69 There was also a positive correlation between drug requirements and alcohol consumption.

Remifentanil

Data on the influence of liver disease on remifentanil kinetics are limited, but in patients, awaiting liver transplantation, Dershwitz and colleagues showed the disposition of the opioid to be unaltered.32 However, in the hepatic dysfunction group the remifentanil concentration needed to depress carbon-dioxide-stimulated ventilation by 50% was significantly reduced (1.56 vs 2.52 ng ml⁻¹).

EFFECT OF RENAL DISEASE

In the healthy patient, most opioid drugs are metabolized to inactive compounds, which are then excreted in the urine or bile. For example, the hepatic bio-transformation of pethidine, alfentanil, fentanyl, sufentanil and morphine may be as high as 80–95%. Phenoperidine differs from these other opioids in that about 50% is normally eliminated in the urine in an unchanged form.

In renal disease, the efficacy of the different opioids may change. The action of phenoperidine, for example, is most likely to be prolonged. Data on opioid efficacy in renal disease are required to prevent opioid dosing that results in significant side effects such as profound analgesia and respiratory depression, so the influence of renal dysfunction on opioid kinetics and dynamics has been evaluated.

Fentanyl, alfentanil, sufentanil and remifentanil

In awake subjects with end-stage renal disease, the kinetics of fentanyl show an increased apparent volume of distribution, and an increased systemic clearance.24 However, Bower found no change in the plasma protein binding of fentanyl in patients,15 such that the findings of Corall and colleagues24 require further confirmation.
Most data from anaesthetized patients with uraemia indicate unaltered fentanyl disposition. \(^{34,48,108}\) Fentanyl undergoes N-dealkylation and hydroxylation, the metabolites appearing in blood within about 1.5 min of dosing. Binding of metabolites is similar to that of the parent drug, and little free fentanyl appears to be excreted unchanged. The possibility of analgesic activity of the nor-metabolite is uncertain.

Studies evaluating alfentanil disposition indicate an increased free drug fraction in anaesthetized uraemic patients,\(^{16,21}\) resulting in greater total drug clearance rates and volumes of distribution but no difference in free drug kinetics.

Although sufentanil is not available for i.v. use in the UK, its disposition is similarly unaltered in end-stage renal disease.\(^{30,42,111}\) There are, however, case reports of prolonged narcosis following administration of sufentanil to patients with chronic renal failure,\(^{40,132}\) in whom this was probably the result of the opioid’s altered dynamics in the uraemic patient.

Recent studies with remifentanil have shown its kinetics to be substantially unaltered in patients with renal disease; there was no change in clearance or volume of distribution, although the elimination half-life was prolonged. Drug dynamics also appeared to be unaffected, with no increased respiratory sensitivity to the drug.\(^{53}\)

Morphine

In 1975, Olsen and colleagues showed that the plasma protein binding of morphine in patients with uraemia was decreased, but the free fraction increased only from 65% to 70–75%.\(^{57}\) There are several reports of prolonged or exaggerated clinical effects when i.v. morphine was given to patients with end-stage renal disease.\(^{33,52,122}\)

Several authors have confirmed that renal failure per se has little effect on morphine parent-drug clearance, but does result in the accumulation of the analgesically active metabolite, morphine-6-glucuronide (M6G).\(^{2,22,104,113,133}\) The higher concentrations of M6G may account for the profound analgesia and sedation seen in uraemic patients who receive large doses of morphine or papaveretum.\(^{39}\)

However, in uraemic patients undergoing transplantation who had received i.v. morphine 10 mg as a supplement to anaesthesia with nitrous oxide (67%) in oxygen, the AUC (area under the concentration–time curve between 0 and 24 h) for morphine was larger than that in healthy anaesthetized patients\(^{150}\) (fig. 4). With the data of Mazoit and colleagues, Sloan and colleagues, and Osborne and colleagues,\(^{9,98,118}\) our data lend support to the view that the kidney may have a role in morphine metabolism. Whereas the papers of Mazoit and Sloan suggest that around 30–35% morphine elimination may be by non-urinary excretion, non-hepatic degradation — that is, potentially by renal parenchymal metabolism — the two studies in patients with renal failure offer another explanation. The increased plasma morphine concentrations (and larger AUC) could have occurred by hydrolysis of one or other of the accumulating glucuronides (probably the 3-glucuronide) back to the parent compound.

The kinetics of the morphine glucuronides have recently been reported by Loetsch and colleagues, who found half-lives for M3G and M6G in healthy volunteers of the order of 2.8–3.2 h and 1.7–2.7 h respectively.\(^{73}\) The longer half-lives of M3G and M6G (41–141 h, and 89–136 h) reported by Osborne and colleagues,\(^{89}\) and Sawe and Odar-Cederlof\(^{104}\) in patients with impaired renal function may be clinically important in the prolonged effect of the parent drug. Furthermore Sawe has shown a significant correlation between the M3G half-life and the plasma urea concentration; while our own data show a significant correlation between the half-lives of both M3G and M6G and the immediate postoperative 24-h creatinine clearance in the patients undergoing transplantation (\(r = 0.87\) and \(r = 0.63\) respectively; \(P < 0.01\) and \(P < 0.05\)). However there are insufficient data to derive a nomogram relating plasma creatinine, predicted or measured creatinine clearance, and accumulation of the active M6G in the patient with renal impairment.

The importance of the 6-glucuronide can also be seen in the case reported by Covington and colleagues,\(^{27}\) where severe respiratory depression was observed in a patient with end-stage renal disease receiving morphine PCA for pain relief after cholecystectomy. The blood morphine concentration was 73 ng ml\(^{-1}\) (within the therapeutic range), but the 6-glucuronide level was significantly elevated at 415 ng ml\(^{-1}\).

What then is the contribution of M6G to the analgesic and depressant effects of morphine? In 14 patients with chronic pain (but normal renal function), Portenoy and colleagues assessed the contribution of the glucuronide to overall analgesia when produced by a morphine infusion.\(^{97}\) Pain relief was greatest when the measured M6G/morphine molar ratio was > 0.7:1, with a significant correlation between the molar ratio and pain relief. In a recent study where volunteers received a tailored infusion of morphine, pain scores were compared with plasma concentrations of both morphine and M6G.\(^{23}\) The time course of the latter correlated best with the pain score against cutaneous electrical stimulation of the finger, so supporting the hypothesis that M6G contributes significantly to the pharmacodynamics of morphine.

In a further study M6G was given intrathecally to provide an analgesic supplement in patients under-
going total hip replacement under spinal bupivacaine anaesthesia. Postoperative analgesia was supplied by a pethidine PCA system. Although there was no difference between treatments (morphine sulphate 500 µg, and M6G 100 and 125 µg) with regard to time to first analgesia demand, total number of demands, or patients having no postoperative demands, there was an improved visual analogue score for analgesia at rest and on movement in the M6G groups. The incidences of nausea and vomiting were similar in all three groups, but respiratory depression requiring treatment was observed in five patients receiving the glucuronide. Hence the efficacy of M6G is clear, but its safety is questionable.

There are also data to suggest that increased concentrations of another morphine metabolite (normorphine) may be responsible for myoclonic activity, but this has not been confirmed by other researchers. Whether the altered kinetics of morphine and its surrogates are the sole explanation of their prolonged dynamic effect is uncertain. Uraemia is itself associated with CNS depression, and the increased sensitivity to CNS depressant drugs may also be attributable to increased receptor responsiveness, or increased meningeal or cerebral permeability or both.

Pethidine

There are fewer kinetic or dynamic data on the disposition of pethidine in patients with renal failure; the drug is mainly metabolized in the liver, with only 1–5% excreted unchanged in the urine. However Chan and colleagues have confirmed the importance of renal function for the excretion of the metabolite norpethidine. In patients with chronic renal failure, repeated doses of pethidine lead to accumulation of the N-demethylated metabolite, norpethidine. This compound has less analgesic but greater convulsant activity than the parent drug, and Szeto and colleagues described two patients in renal failure where increased plasma ratios of norpethidine/pethidine were associated with excitatory signs.

New drugs

Despite the advances made through the developments of fentanyl, alfentanil, sufentanil and remifentanil, further powerful and potent opioids have been evaluated over the past 5 years, including A3665 (trepainifentanil); a phenylpiperidine derivative, mirfentanil (a piperidine opioid with both agonist and antagonist properties); and tradamol.

A665 (TREPIFENTANIL)

This piperidine opioid acts preferentially at the µ receptor. In a comparison of A3665 with alfentanil in volunteers, Cambareri and colleagues evaluated its analgesic efficacy and ventilatory depression. The two drugs appeared to be approximately equipotent. At doses up to 32 µg kg⁻¹, the test drug causes significant analgesia with a peak effect seen about 3 min after dosing. However, the effect of alfentanil appeared longer-lasting than that of the A3665. At doses of 32 µg kg⁻¹ and above there was significant respiratory depression, resulting in significant decreases in oxygenation and increases in carbon dioxide tension in the blood. The peripheral tissue oxygenation also declined to below 90%, although cardiovascular stability was noted at all doses.

Lemmens and colleagues have carried out formal kinetic-dynamic modelling, using the EEG as a surrogate end-point for drug effect. Using these data, computer simulations of recovery after infusions of different duration suggest that A3665 may have significant advantages over alfentanil and fentanyl, but probably not over remifentanil; the times for a 50% decrease in the effect-site concentration range between 60 and 80 min for infusions of alfentanil lasting 4–10 h, but only 15–30 min for A3665. The blood–brain equilibration time of A3665 was slightly longer than that of alfentanil (1.2 vs 0.6 min), but both equilibrated faster than fentanyl.

MIRFENTANIL (A3508)

In animal studies, A3508 produced dose-dependent changes in analgesia, but a "ceiling" effect on ventilatory depression. An initial volunteer study evaluated doses of mirfentanil between 12.5 and 400 µg kg⁻¹ and compared them with fentanyl 0.75–3 µg kg⁻¹. Mirfentanil showed both analgesic and respiratory depressant effects, but no significant changes in any cardiovascular parameter. However when compared with fentanyl in equipotent analgesic doses, mirfentanil showed a flatter dose–response curve with less depression of ventilation (measured as the increase in arterial carbon dioxide tension). In a subsequent study where mirfentanil was used to provide "conscious sedation," after subarachnoid blockade, incremental doses of 75 µg kg⁻¹ i.v. were given until the patients' speech became slurred (at a total dose of 9.5 mg, and an associated blood concentration of about 190 ng ml⁻¹). This sedation was accompanied by a further reduction in both mean arterial pressure and heart rate, and there was a decrease in the respiratory rate from 15 to 11 breaths per minute. Oxygen saturation decreased statistically but not clinically (97.7% to 96.1%); however the end-tidal carbon dioxide level did not change.

In a separate patient study using the opioid for conscious sedation, mirfentanil caused antegrade amnesia (as assessed using a yes–no recognition task), coupled with evidence of post-drug impairment of psychomotor activity (using the p-deletion and digit-symbol substitution tests). Dynamic–kinetic evaluation was again carried out using the EEG as the surrogate end-point measure of drug effect, with butorphanol used as a "control" for comparison of mixed agonist-antagonist drug effects. With both drugs there were significant side-effects: nausea and hallucinations and, with mirfentanil, two cases of epileptiform activity on the EEG, with one of the volunteers progressing to a generalized convulsion.

Both mirfentanil and butorphanol caused a significant tachycardia and ventilatory depression. Mirfentanil (when infused at a rate of 25 µg kg⁻¹ min⁻¹) had greater cardiovascular effects during and after drug dosing. The kinetics of mirfentanil showed an elimination half-life of around 300 min, clearance of 5.8 l min⁻¹, and apparent volume of distribution at steady state of 247 l.
Recent advances and developments during the clinical use of i.v. opioids during the peroperative period

Because of the marked inter-individual variability in the EEG patterns with both drugs and, in the case of mirfentanil, an absence of slowing of cerebral rhythms, it was not possible to use the EEG as a measure of analgesic action on the brain. Data obtained after this study was completed indicate that mirfentanil is not a mixed agonist-antagonist, but rather a partial μ, partial delta, and negligible kappa opioid agonist. Because of these significant and serious cardiovascular and CNS effects, mirfentanil is not being further evaluated.

Tramadol

Tramadol is another phenylpiperidine derivative, with a structure similar to that of pethidine. The limited kinetic data of the drug show an elimination half-life of 5–7 h, and clearance of 7–10 ml kg⁻¹ min⁻¹. It is a drug that binds to sigma and kappa receptors with weak affinity as well as to the μ receptor, where it exerts moderate activity. Tramadol also has actions at the monoamine receptors of the sympathetic nervous system, where it acts to prevent amine re-uptake, as well as possibly displacing stored 5-HT from nerve endings.

Tramadol exists as a chiral mixture, and there are separate identifiable actions of the different stereoisomers, namely the (+) isomer seems to bind to the μ receptor, while the (−) isomer is responsible for monoamine re-uptake inhibition. Through this dual action, the analgesic activity is only partially antagonized by naloxone; there is also partial inhibition of analgesia by two antagonists (such as yohimbine) and serotoninergic blockers.

On comparison with morphine, tramadol has a potency of about 1/5th to 1/10th but causes less respiratory depression. In a randomized, double-blind comparison with extradural morphine when used to provide analgesia after thoracotomy, James and colleagues found no differences between the treatments provide analgesia after thoracotomy.

References


4. Anesthesiology


Recent advances and developments during the clinical use of i.v. opioids during the peroperative period


