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Review

Human pharmacokinetics of analgesics and methods for their determination in biological fluids

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Abstract: The main pharmacokinetic data of analgesics — biological half-lives, apparent volumes of distribution, total body clearances — obtained in humans, and their clinical relevance are summarized. Special emphasis has been given to the analytical methods used for the quantitative determination of these drugs in biological fluids.

Keywords: *Morphine; codeine; pethidine; methdone; pentazocine; buprenorphine; ketamine; salicylic acid derivatives;* p-*aminophenol derivatives; bioavailability; plasma clearance; pharmacokinetics; drug half-lives; volume of distribution.*

It is generally accepted that the plasma concentration of analgesics best reflects the effects of these drugs, i.e. that there exists a minimal effective plasma concentration that is needed for the analgesic effect. The goal of the clinician is to maintain this concentration with the smallest possible fluctuation. According to this concept the best approach to pain relief would be constant rate intravenous (i.v.) infusion. In practice this treatment can only be carried out in cases of acute pain under the physician's surveillance. The problems of intermittent treatment are the following:

analgesics applied orally are subject to 'first-pass' metabolism, and hence the bioavailability is different;

the pain sensation of the patients is different which is manifested in the deviation of the mean effective plasma concentration (MEC);

protein binding: both plasma and tissue protein binding may be different due to the pathological state and the interaction with other drugs;

the functional state of the liver and kidneys should also be taken into consideration;

there are analgesic drugs that have active metabolites.

Knowledge of the pharmacokinetic parameters may help the physician in adjusting the proper dosage regimen in individual patients.

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Morphine-related Narcotics

Morphine

Morphine is widely used for the relief of severe pain. It has been used for more than a century and is still considered as the reference drug among narcotic analgesics.

Kinetics. Both after parenteral and oral administration the absorption of the drug is rapid; peak plasma levels occur after about 30 min [1]. The plasma half-life of morphine has been estimated at 1.9–3.1 h, with essential agreement among different authors. The apparent volume of distribution was 3.2 ± 0.3 l kg^{-1} and plasma clearance was 14.7 ± 0.9 ml min^{-1} kg^{-1} after intravenous administration of the drug [2]. After intramuscular administration the systemic availability is complete vs intravenously administered morphine, but following oral administration the absorption is incomplete due to a 'first-pass' effect. Therefore the plasma levels after this application are only ⅓–⅕ of those after parenteral injection [3]. Morphine distribution is significantly altered by anaesthesia and major surgery. For preoperative subjects the distribution volume was 6.3 ± 3.6 l kg^{-1} and the terminal half life was 3.8 ± 2.3 h (mean ± S.D.). In the postoperative period the values decreased to 3.7 ± 1.4 l kg^{-1} and 2.2 ± 1.1 h. Plasma clearance remained constant; preoperative and postoperative values of 20 ± 7.0 and 21 ± 6.0 ml min^{-1} kg^{-1} respectively [4]. Observations have suggested that age is a factor in morphine analgesia [5] and kinetics. The plasma clearance and apparent volume of distribution was less in older subjects than in younger ones, and the calculated concentration of morphine in the peripheral compartment was higher in the elderly for 1.5 h after dosing [6]. On the other hand, there did not seem to be any difference between children of different ages in their sensitivity to morphine [7].

Morphine is eliminated mainly by metabolism; the major metabolites are morphine glucuronides. About 10% of the dose is excreted as unaltered morphine after parenteral administration, and 3% after oral administration of the drug [3]. Approximately 35% of the drug is protein-bound, primarily to the albumin fraction [8].

Routes of administration and dosage. Hypodermically, 10 mg/70 kg of body weight is generally considered to be an optimal initial dose of morphine. Subsequent doses may be higher or lower, depending on the analgesic response and the side effects produced. The average oral dose of morphine is often stated as 8–20 mg. However, controlled studies have shown that oral administration is only about one-sixth to one-fifteenth as effective as parenteral administration (depending on whether peak or total analgesia is measured). Intravenous morphine can be used for preoperative medication, for minor surgical procedures when general anaesthesia is not indicated, for severe cardiac pain, for pulmonary edema and for severe biliary and renal colic. The usual i.v. dose is 2.5–15 mg. When postoperative pain was relieved by patient-controlled administration of i.v. doses of morphine by means of a programmable drug injector, the computer-calculated mean minimum effective concentration was 16 ± 9 ng ml^{-1}. The mean morphine consumption was 2.6 ± 1.2 mg hr^{-1} which produced a mean plasma concentration of 21 ± 12 ng ml^{-1} [4].

Analytical techniques for the determination of morphine in human plasma include radioimmunoassay (RIA) [1] and gas–liquid chromatography with an electron capture detector [7]. These methods have a limit of detection of *ca.* 1 ng ml^{-1}.

Codeine

Codeine is chemically related to morphine. It is widely used — usually in combination with other analgetic compounds in the relief of moderate pain.

Kinetics. Following intramuscular administration of 65 mg codeine, peak plasma concentrations (194–340 ng ml^{-1}) were observed between 0.25 and 1 h. After oral dosing (65 mg codeine in an analgesic mixture which also contained aspirin, phenacetin and caffeine) peak plasma codeine concentrations (102–140 ng ml^{-1}) appeared within 0.75–1 h. Oral bioavailability of codeine was 42–71% (mean 53%). The mean plasma half-life and volume of distribution of codeine after intramuscular (i.m.) injection were 3.32 h and 5.1 l kg^{-1}, respectively. The mean plasma clearance was 0.73 ± 0.05 l kg^{-1} h^{-1} [9]. The hypothesis that codeine may exert its moderate analgesic potency through partial biotransformation to morphine could not be proved due to a lack of analytical technique of sufficient sensitivity and specificity. Using RIA, plasma concentrations of codeine and morphine could be determined following oral administration of codeine. After administration of codeine phosphate (60 mg) in combination with aspirin (650 mg) or paracetamol (600 mg) to two separate groups, mean peak codeine plasma concentrations and elimination half-lives were 159 ng ml^{-1} and 2.9 h, and 138 ng ml^{-1} and 2.4 h, respectively. Mean maximum concentrations of metabolically produced morphine were 6.8 ng ml^{-1} and 7.4 ng ml^{-1}. The results support the hypothesis that metabolically produced morphine may influence or be responsible for the analgesic efficacy of codeine [10]. Once absorbed, codeine is metabolized by the liver and excreted chiefly in the urine. Conjugation of codeine has been reported to be a major route for its metabolism [11].

Routes of administration and dosage. Codeine, in contrast to morphine, is approximately two-thirds as effective orally as parenterally, both as an analgesic and as a respiratory depressant. Its greater oral efficacy is due to reduced 'first-pass' metabolism in the liver, presumably due to the presence of a methoxy group in position 3, the principal site of metabolism of morphine. The usual oral dose is 60 mg every 4–6 h.

Analytical methods for determination of codeine from human plasma include gas-chromatography–mass spectrometry [12], spectrophotometry on thin-layer chromatography plates [13] and radioimmunoassay [10]. Using RIA as little as 1.5 ng/ml of codeine can be detected in plasma.

Phenylpiperidine Analgesics

Pethidine

Pethidine is a potent narcotic which is widely used as an analgesic and as a premedicant prior to anaesthesia.

Kinetics. Pethidine is absorbed by all routes of administration but its oral bioavailability is only about 50% (47–73%) because of its 'first-pass' metabolism. Therefore it is widely used parenterally. Intramuscular administration of 25 mg pethidine to healthy subjects resulted in complete and rapid absorption of the drug. The elimination half-lives were between 4.8 and 9.4 h, the plasma clearance was 472–686 ml min^{-1} [14]. The oral bioavailability of pethidine was 48–56%, the terminal half-life 4.1 ± 1.6 h and the clearance 870 ± 400 ml min^{-1} [15]. Its elimination occurs chiefly in the liver; the major

metabolites in man are norpethidine, pethidinic and norpethidinic acids and their conjugates. Norpethidine is about half as active as pethidine in its analgesic effect, and twice as potent as a convulsive agent; other metabolites are inactive [16, 17]. Renal excretion of pethidine and norpethidine are pH-dependent, about 15–30% of the dose is excreted as pethidine and norpethidine [16].

Pethidine can be used in any situation where an opioid analgesic is required. However, there are a number of clinical conditions in which its reduced spasmogenic effects or its better oral efficacy make pethidine preferable to morphine. The pattern of overall incidence of untoward effects that follow the use of pethidine are similar to those observed after equianalgesic doses of morphine, except that consumption and urinary retention are less common.

Therapeutic plasma level and dosage. When pethidine was administered by continuous intravenous infusion (24 mg h^{-1}) the mean pethidine plasma concentration associated with zero pain was 590 ng ml^{-1} in 10 patients [18]. Similar results were found in another study where surgical patients were allowed to self-administer small intravenous doses of pethidine to relieve pain after surgery. Injections were given by means of a programmable drug injector. Pethidine consumption was 26 mg h^{-1} and the mean measured plasma concentration was 551 ± 182 ng ml^{-1}. The computer-calculated minimum effective plasma concentration averaged 455 ± 174 ng ml^{-1} [19]. The analgesic plasma level of pethidine in women in labour was 200–400 ng ml^{-1} [20]. In summary the traditionally used intermittent i.m. injection of the drug brings inconsistent pain relief because of the narrow concentration range between no analgesia and complete suppression of pain. The administration of pethidine by continuous i.v. infusion (25 mg h^{-1}) appears to be effective and rational in the treatment of pain.

Pethidine plasma concentrations can be determined by GLC [21]. The detectable amount of pethidine in 1 ml plasma is about 5 mg at the fifth hour after the administration.

Fentanyl

Fentanyl is a potent, short-acting narcotic analgesic but prolonged and recurrent respiratory depression has been reported in man [22].

Kinetics. The popularity of the use of fentanyl is due largely to the rapid onset and short duration of action, and the potency of the drug which is about 150 times that of morphine. The elimination half-life of fentanyl after an intravenous dose of 6.4 μg kg^{-1} was 219 ± 10 min. The apparent volume of distribution was 3.99 ± 0.2 l kg^{-1} and the plasma clearance was 956 ± 65 ml min^{-1}. Elimination of fentanyl occurred mainly by biotransformation: less than 8% of the dose was excreted unchanged in the urine [23]. The pharmacokinetic parameters of fentanyl were determined in another study using RIA for the determinations. After high doses (0.5 or 1 mg m^{-2}) administered intravenously, the half-life was 346.5 min. After i.v. doses of 0.1 mg m^{-2}, the half-life was 86.6 min. At all doses, plasma levels fell rapidly in the first 5 min to approximately 20% of the peak value. After 2 h serum levels stabilized at low values (1.5 and 8.0 ng ml^{-1}). Urinary excretion of fentanyl accounted for 15–20% of the administered dose [24].

Therapeutic uses. Fentanyl is usually used only as an intravenous anesthetic in combination with droperidol.

Analytical methods. Fentanyl can be detected in human plasma by RIA [24] which allows monitoring for at least 6 h; the sensitivity of the method is about 1.2 ng ml^{-1}. Using tritium-labelled fentanyl [23], 0.3 ng of the drug could be determined in 1 ml plasma.

Ketobemidone

Ketobemidone is a pethidine-like strong narcotic analgesic.

Kinetics. Although ketobemidone has been extensively used in the treatment of pain for more than 30 years there have been few studies of its pharmacokinetics. Its elimination half-life was 2.25 ± 0.35 h, its plasma clearance ranged from 0.25 to 0.88 l h^{-1} kg^{-1} with a mean of 0.55 ± 0.2 l h^{-1} kg^{-1}, and the apparent volume of distribution was 1.80 ± 0.74 l kg^{-1}. The oral bioavailability showed marked variation ranging between 17 and 62% (mean 34 ± 16%) [25]. Major surgery affects the pharmacokinetics of ketobemidone. The preoperative terminal half-life was 3.9 ± 1.7 h, and the apparent volume of distribution was 5.9 ± 2.6 l kg^{-1}. In the postoperative period the distribution volume decreased to 3.7 ± 0.4 l kg^{-1} and the half-life decreased to 2.1 ± 0.4 h. Plasma clearance did not change significantly, being 18 ± 4.3 ml min^{-1} kg^{-1}, and 22 ± 7.5 ml min^{-1} kg^{-1} respectively [26]. The rectal bioavailability of ketobemidone was found to be *ca* 44%. The elimination half-life increased to 3.27 h after rectal administration of the drug, indicating a contribution from late absorption [27].

When the effect of ketobemidone in postoperative pain was investigated by patient-controlled intravenous administration using a programmable drug injector, it was found that the mean ketobemidone consumption was 2.3 ± 0.8 mg h^{-1}, which produced a mean plasma concentration of 28 ± 11 ng ml^{-1}. The computer-calculated mean minimum effective concentration was 25 ± 11 ng ml^{-1} [26]. The analgesic potency of ketobemidone is claimed to be of the same magnitude as that of morphine. The duration of its analgesic effect is about 5–7 h.

Ketobemidone can be determined in human plasma by GC–MS [28].

Diphenylheptan Derivatives

Methadone

The primary uses of methadone are relief of pain, treatment of opioid abstinence syndromes, and treatment of heroin users.

Kinetics. The main pharmacokinetic parameters of methadone are rather variable in opiate-dependent subjects. The elimination half lives were 8.5–47 h (mean S.D. 28.1 ± 10.9). The apparent volumes of distribution varied from 2.1 to 5.6 l kg^{-1} (mean S.D. 3.92 ± 1.09). The body clearances varied between 0.96 and 6.1 ml min^{-1} kg^{-1} with a mean of 2.08 ± 1.71 ml min^{-1} kg^{-1}. Five patients had a bioavailability exceeding 90% and three had lower bioavailabilities of between 41 and 76% [29]. The methadone half-life in methadone maintenance therapy was 52 ± 20 h [29], the plasma clearance was 183.7 ± 23.52 ml min^{-1} [31]. The marked individual variation in methadone pharmacodynamics and kinetics requires an individually optimized dosage regimen. The protein binding of methadone is high (*ca* 90%) and α_1-acid glycoprotein is the main determinant of the free fraction in plasma [32]. Because of their elevated concentrations of plasma α_1 acid glycoprotein, cancer patients had a lower level of free methadone in

plasma than did members of a control group [33]. Metabolism of methadone occurs extensively in the liver. The main urinary metabolite is 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine [34]. At low urine pH, the renal clearance of the drug markedly increased; urinary pH is a major factor in the renal excretion of unchanged methadone [31]. Methadone is often used for the treatment of opiate-dependent subjects in maintenance therapy. During chronic treatment a dispositional tolerance is developed, and a self induction of the metabolism of methadone would lead to a faster rate of elimination and therefore lower steady state plasma levels. Other mechanisms which must be considered are enhancement of first-pass metabolism and increased extravascular binding of methadone on multiple dosage. The best record of rehabilitation was obtained in subjects discharged with steady-state plasma concentrations above 200 ng ml^{-1} [35].

Therapeutic use and dosage. The pharmacological actions of single doses of methadone are qualitatively identical to those of morphine. The outstanding properties of methadone are its effective analgesic activity, its efficacy by the oral route, its extended duration of action and its tendency to show persistent effects with repeated administration. The oral analgesic dose for adults is 5–15 mg depending on the severity of the pain and the response of the patient. The initial parenteral dose is usually 5–10 mg.

Methadone plasma levels can be determined by GC–MS [30, 36] or GLC methods [31]. Using a modified GC–MS method [29], 0.05 μmol l^{-1} of methadone was detected in human plasma.

Propoxyphene and norpropoxyphene

Propoxyphene is an effective oral analgesic, structurally related to methadone. Of the four stereoisomers, only the alpha racemate, known as propoxyphene, has analgesic activity.

Kinetics. After a single 130 mg oral dose, the propoxyphene half-life was 3.3 h, plasma clearance was 994 ml min^{-1}, and the apparent volume of distribution was 178 l. The half-life of norpropoxyphene in the same study was 6.1 h, the plasma clearance was 454 ml min^{-1}, and the volume of distribution of norpropoxyphene was 319 l [37]. After single oral doses of propoxyphene at 65, 130 and 190 mg and after slow intravenous infusion of 65 mg the kinetic parameters were: oral clearance of propoxyphene 1300–3600 ml min^{-1}, systemic clearance 600–1200 ml min^{-1}, apparent volume of distribution 700–1800 l. Propoxyphene half-life was 8–24 h, and norpropoxyphene half-life ranged from 18 to 29 h. The drug was reported to have first-pass elimination; the systemic availability was reduced [38]. Several changes in propoxyphene and norpropoxyphene kinetic occurred during repeated dosing with propoxyphene (13 consecutive oral doses of 130 mg). Propoxyphene plasma clearance decreased to 508 ml min^{-1}, half-life increased to 11.8 h and volume of distribution increased to 235 l. Similar changes in norpropoxyphene kinetics could be observed. Propoxyphene and norpropoxyphene accumulated during repeated dosing. When the effects of the first and thirteenth doses (130 mg propoxyphene) were compared after 8 h, the plasma concentration of propoxyphene had increased by about 500% and that of norpropoxyphene rose by *ca* 700% [37]. Studies have shown that propoxyphene is primarily eliminated by hepatic metabolism. The major metabolic pathway is demethylation to norpropoxyphene, which is in large part eliminated by renal excretion. Ring hydroxylation and glucuronide formation are less

important pathways [39]. Norpropoxyphene is a weakly opiate-active and potentially toxic substance. Propoxyphene is subject to significant 'first-pass' metabolism in the liver. Variations in 'first-pass' elimination as a result of disease, repeated dosing or concurrent administration of other drugs may result in extensive accumulation of propoxyphene and norpropoxyphene. In some patients this will result in serious toxicity. Therefore propoxyphene should be administered cautiously and in reduced doses to patients with hepatic dysfunction [40] and to patients with renal insufficiency [41].

Therapeutic uses. The only recognized use of propoxyphene is for the treatment of mild to moderate pain that is not adequately relieved by aspirin. When appropriate doses are selected, combinations of aspirin and propoxyphene can be as effective as the combination of codeine and aspirin.

Propoxyphene and norpropoxyphene can be determined in human plasma by GLC [42] or GC–MS methods [38, 43]. 8 ng of propoxyphene can be detected in 1 ml plasma using a modified GLC method [40]. The sensitivity of the GC–MS method is 8–10 nmol ml^{-1} and the decrease of the plasma concentration can be followed for 70 h.

Mixed Function Agonist–antagonist Agents

The narcotic agonist–antagonist drugs show overall pharmacokinetic similarity in having clearance values greater than 1000 ml min^{-1}, which exceeds the liver blood flow. Agents such as β-blockers and halothane which lower hepatic blood flow will decrease the clearance of these drugs. High clearance predictably leads to a substantial first-pass effect and hence low oral bioavailability. In clinical practice the advantages of mixed agonist–antagonists are low-dependence liability and a ceiling effect for respiratory depression particularly.

Pentazocine

Pentazocine is one of the many compounds synthesized as part of a deliberate effort to develop an effective analgesic with little or no abuse potential. Pentazocine seems to fulfil these requirements relatively well; only a few cases of abuse have been reported.

Kinetics. The average beta phase half-life is 177 ± 34 min after intravenous administration of 30 mg pentazocine. The total volume of distribution is 5.56 ± 1.63 l kg^{-1}, plasma clearance being 1.38 ± 0.32 l min^{-1}. Oral bioavailability was found to be 18.4 ± 7.8%. This low bioavailability can be explained by the 'first-pass' elimination of pentazocine following oral administration [44]. The plasma protein binding of the drug is 50–60% in healthy subjects [45].

Pond *et al.* used doses of 0.4 mg/kg (i.v.) and 0.8 mg/kg (oral). The measured oral bioavailability was 21 ± 7%. The biological half-life was 342 ± 84 min and the blood clearance 768 ± 130 ml min^{-1}. In patients with alcoholic cirrhosis the clearance was 48% lower and bioavailability 233% greater than in normal subjects [46].

Pentazocine was found to be extensively metabolized: less than 13% of the dose appeared in the urine unchanged and 12–30% was excreted as a glucuronide conjugate [47].

Therapeutic uses. The analgesic effect after 45 mg/70 kg pentazocine administered intramuscularly is generally maximal between 30 and 60 min and lasts for 2–3 h. After a

single dose of 20–25 mg/70 kg intravenously, peak analgesia occurred between 15 and 45 min and lasted for about an hour. Oral pentazocine is about one-third to one-fourth as potent as i.m. pentazocine [48]. The pattern of CNS effects is generally similar to that of the opioids, including analgesia, sedation and respiratory depression. The cardiovascular responses to pentazocine differ from those seen with the morphine-like opioids, in that high doses cause an increase in blood pressure and heart rate.

Dosage. In terms of analgesic effect, a 30–50 mg dose given parenterally is approximately equivalent to 10 mg of morphine. An oral dose of about 50 mg of pentazocine results in analgesia equivalent to that produced by 60 mg codeine. Because abuse patterns appear to be less likely to develop with oral administration, this route should be used whenever possible. Pentazocine can be measured in human plasma fluorimetrically [48]. The limit of detection is about 15 ng ml^{-1}.

Buprenorphine

Buprenorphine is a synthetic opioid derived from thebaine with mixed agonist–antagonist properties and a low abuse potential.

Kinetics. The pharmacokinetic parameters after intravenous administration of 0.3 mg buprenorphine were: elimination-half-life 183.6 ± 37.0 min; plasma clearance 1275 ± 88.9 ml min^{-1}; apparent volume of distribution was 187.8 ± 35.3 l. The parameters were very similar after i.m. administration of 0.3 mg buprenorphine: half-life 138.5 ± 41.8 min; plasma clearance 992.7 ± 70.3 ml min^{-1}; volume of distribution 148.1 ± 51.3 l. Comparison in the same patient, awake and anesthetized, showed that the plasma clearance was significantly lower in the anesthetized state. Buprenorphine is almost completely metabolized *in vivo*; the clearance obtained is thus very close to the expected hepatic blood flow under the anesthetic conditions. The effects of the drug far outlasts the plasma level and there is no direct relationship between plasma level and pharmacologic effect [49].

Dosage. Buprenorphine is about 25–50 times more potent than morphine. The usual dose is 0.3–0.6 mg given every 6–8 h. The analytical method for determination of buprenorphine is RIA [49]. Using this method, 0.4 ng of the drug can be measured in 1 ml plasma.

Butorphanol

Pharmacokinetic data for butorphanol are limited. No information is available from long-term studies. A terminal plasma half-life of 158.7 ± 5.5 min has ben reported in a study [49] which monitored the drug for up to 8 h. The plasma clearance of approx. 2700 ml min^{-1} was calculated for a 70 kg man [51]. This is greater than the normal hepatic blood flow, and probably reflects a high red blood cell: plasma partition. The same source quotes an apparent volume of distribution of 350 l for a 70 kg man. The major route of elimination of butorphanol in man was renal (75%) with biliary elimination accounting for about 15% of the dose. Butorphanol is bound about 80% to plasma proteins [52].

Pharmacodynamic considerations. The analgesic effect of i.m. butorphanol was dose-related over the range 1–4 mg, and the side effects (drowsiness, sleepiness) were also

shown to be dose-related [53, 54]. The RIA method used in these studies [50] was both sensitive and specific.

Nalbuphine

After parenteral administration of usual doses this drug is approximately equipotent in its analgesic activity to morphine. Only very limited data are available on the disposition of nalbuphine in man. After i.m. administration nalbuphine is rapidly absorbed. Peak plasma concentrations (mean 48 ng ml^{-1}) are reached within 30 min after a 10 mg i.m. dose. The terminal half-life is about 5 h in healthy subjects. Both metabolites and unchanged drug have been identified in the urine, the largest proportion of the dose being excreted as an inactive glucuronide conjugate [51, 55]. The ratio of equianalgesic parenteral to oral doses of nalbuphine suggests substantial 'first-pass' biotransformation.

Therapeutic use. Nalbuphine has been effectively used in moderate to severe postoperative pain, as well as in pain of various other aetiologies [55]. The recommended parenteral doses of nalbuphine are 10 mg per 70 kg body weight, which may be repeated every 3–6 h as needed. The maximum recommended single dose is 20 mg with the total daily dose not exceeding 160 mg. Nalbuphine can be determined in human plasma by HPLC [56].

Ketamine

Ketamine is widely used to induce and maintain anaesthesia in adults and in children. In lower doses ketamine also has analgesic properties, and it has been used in post-operative pain relief. Ketamine kinetics appears to follow at least a three-term exponential decay, corresponding to a three-compartment open model. The main pharmacokinetic parameters after 2.2 mg kg^{-1} i.v. administration of ketamine are: elimination half-life 2.25 ± 0.45, apparent volume of distribution in the steady state: 1.78 ± 0.74 l kg^{-1} and plasma clearance 0.848 ± 0.316 l min^{-1} [57]. The pharmacokinetic parameters of the drug did not differ significantly after i.v. or i.m. injection. The mean plasma half-life of the drug following i.v. injection of 25 mg kg^{-1} was 186 min and total body clearance was 19.1 ml min^{-1} kg^{-1}. Absorption after i.m. administration was rapid and the bioavailability was 93%. However, only 17% of the oral dose was absorbed. The low plasma ketamine concentrations after oral dose could have been due to incomplete absorption or to extensive first-pass metabolism [58]. There is an observation that the elimination half-life of ketamine is shorter in children [59].

Dosage. I.v. anaesthetic doses of ketamine were found to be 2.5 mg kg^{-1} in patients. It can also be given intramuscularly (6–10 mg kg^{-1}) and this route is used extensively in children. The analgesic doses were found to be 0.125 or 0.25 mg kg^{-1} i.v. There was a significant correlation between the plasma ketamine concentration and the analgesic activity of the drug. Pain threshold elevation occurred at plasma ketamine concentrations above 160 ng ml^{-1} [58].

Analytical methods for measurement of ketamine in human plasma include GLC [58] and GC–MS [60].

Peripherally-acting Oral Analgesic Agents

The primary action of these drugs appears to be in inhibiting the cyclo-oxygenase enzyme system that metabolises arachidonic acid to its endoperoxide intermediates. The

endoperoxides are biosynthesised to thromboxanes, prostacyclines and prostaglandins. Various intermediates and end products of the arachidonic acid cascade interrelate with other local mediators such as bradykinin, histamine and 5-hydroxy-tryptamine to promote erythema, oedema and pain. Some evidence suggests that these agents may have secondary effects of cyclo-oxygenase inhibition within the CNS [61, 62].

Propionic Acid Derivatives

Naproxen

Naproxen is a propionic acid derivative with analgesic and anti-inflammatory activity which has been widely used in the treatment of rheumatic disorders.

Kinetics. Naproxen is completely absorbed after oral administration [63]. The plasma half-life of the drug is 12–15 h and is not affected by the dose or continuous administration [64]. Concomitant oral probenecid (4 × 500 mg/day) increases plasma levels and half-life from 14 to 37 h [65]. Naproxen has an apparent volume of distribution of 6.3 l and is 90% bound to plasma proteins. Naproxen is largely biotransformed by the liver; about 10% of the dose is excreted unchanged by the kidney.

Therapeutic uses. Naproxen in single doses of 250–750 mg has been shown to be an effective analgesic in patients with moderate or severe postoperative pain resulting from orthopaedic, dental, vascular and other surgical procedures [66], and in cases of sport injuries, trauma and dysmenorrhoea [67]. The efficacy of naproxen in relieving postpartum uterine pain was demonstrated in two separate well-designed placebo-controlled trials [68]. The analgesic effect after 600 mg oral naproxen occurred for from 2 to 8 h.

Dosage. Naproxen has generally been well tolerated during both short- and long-term studies. Gastrointestinal complaints and central nervous system effects have been the most commonly reported side-effects, but have been less of a problem than with aspirin or indomethacin. The usual starting dose and maintenance dose of naproxen is 250 mg twice daily. Dosage adjustment is not required in cases of renal insufficiency [69].

Analytical methods for the determination of naproxen in human plasma include fluorimetry [69, 70], GLC [71, 64] and HPLC [72, 76]. The sensitivities of the HPLC methods were 40 ng ml^{-1} [72] and 2 ng ml^{-1} [76].

Ketoprofen

Ketoprofen is a new nonsteroidal anti-inflammatory drug and is used primarily in the treatment of rheumatoid diseases.

Kinetics. The pharmacokinetic parameters after single oral, intramuscular and rectal doses, and after repeated oral doses, were: the elimination half-life ranged from 1.13 to 1.27 h, and the apparent volume of distribution was approximately 10–15% of body weight. The plasma clearance after oral administration was 1.16 ± 0.09 ml min^{-1} kg^{-1}, after i.m. administration 1.21 ± 0.07 ml min^{-1} kg^{-1}, and after rectal administration 1.42 ± 0.10 ml min^{-1} kg^{-1}. A mean of 71–96% of the oral dose and 73–93% of the intramuscular and rectal dose was estimated to be systemically available. The mean steady state concentration of ketoprofen in plasma ranged from 0.43 to 5.62 μg ml^{-1},

the accumulation ratio was 1.08 ± 0.08. The projected cumulative excretion of total (free plus conjugated) ketoprofen via urine exceeded 63–75% of the dose, of which approximately 90% was ketoprofen glucuronide [73].

Similar kinetic parameters were observed after 50 mg oral administration of ketoprofen: the peak plasma concentrations were between 140 and 170 μg ml^{-1}, reached after 45 min. The elimination half-life was 91.5 min, the apparent volume of distribution 8.06 ± 1.49 l and plasma clearance 86.9 ± 18.8 ml min^{-1} [74]. Clinical studies of efficacy in patients with rheumatoid arthritis have demonstrated that ketoprofen is superior to placebo and approximately equal, at doses of 75–200 mg day^{-1}, to indomethacin (75–150 mg day^{-1}) and aspirin (3.6–4.0 g day^{-1}) [74]. Ketoprofen given intramuscularly to patients with chronic arthritis on the day after elective joint surgery, or during bouts of extreme pain, resulted in satisfactory pain relief for up to 8 h after administration.

Dosage. The suggested therapeutic dose of oral ketoprofen is 4 × 50 mg day^{-1}.

Analytical methods. Ketoprofen can be determined in plasma either by GLC [75] or HPLC [75, 77]. Using GLC 0.2 μmol l^{-1} ketoprofen can be detected 7 h after administration. The sensitivities of the HPLC methods are 10 ng ml^{-1} to 1 μg ml^{-1} in human plasma.

Indoprofen

Indoprofen is an indole propionic acid. It diffuses poorly through the blood–brain barrier, and thus has weak antipyretic activity.

Kinetics. After oral administration, indoprofen is rapidly absorbed, its elimination half-life is estimated to be about 2 h. It is approximately 98% protein-bound. Within 24 h, 80% of the administered drug excreted in the urine primarily as the glucuronide metabolite [78].

Therapeutic uses. Indoprofen has given relief in a variety of painful conditions including cancer, postpartum, postsurgical and dental surgery [79–82]. In these studies indoprofen appeared to have an analgesic effect for 6 h. They also supported the conclusions that indoprofen in a dose of 50–200 mg is an effective analgesic in a variety of painful conditions. The dose response is evident between 50 and 100 mg. The studies indicated that 100 mg is the optimal analgesic dosage of indoprofen. Overall indoprofen appears to be a safe and effective analgesic in the dosage range of 50–200 mg every 4–6 h. Both its peak effect and duration of activity appear significantly better than usual dosages of aspirin or paracetamol.

Indoprofen can be measured in plasma by GLC [83]; 0.8–1 μg ml^{-1} of the drug can be measured.

Fenbufen

Fenbufen is a new propionic acid derivate that exhibits anti-inflammatory, analgetic and antipyretic properties in man.

Kinetics. After a single oral dose of 600 mg fenbufen it appeared in the plasma after a lag time of 0.45 h; a peak plasma concentration of 5.97 μg ml^{-1} was observed after

1.19 h. The half-life of plasma disappearance was 10.26 h [84]: a similar value of the elimination half-life (11.3 h) was observed in another study. The elimination half-life of the drug was not affected by renal insufficiency [85]. These values suggest that a single oral dose of fenbufen in man should produce a long-lasting therapeutic effect. Fenbufen is extensively metabolized in the liver to four major metabolites. Both γ-hydroxy-4-biphenyl butyric acid and 4-biphenylacetic acid have a similar anti-inflammatory activity to that of fenbufen. The two main inactive metabolites are γ-4-dihydroxy(1,1 biphenyl)-4-butanoic acid, and 4-hydroxy(1,1-biphenyl)-4-acetic acid. The plasma levels of the active metabolites of fenbufen are relatively high 48 h after administration. This phenomenon would explain the long therapeutic activity of the drug [80].

Analytical methods. Using GLC [86], 0.2 μg fenbufen can be measured in 1 ml plasma. The sensitivity of an HPLC method [87] is 0.5 μg ml^{-1} in plasma.

Salicylic Acid Derivatives

Acetylsalicylic and salicylic acid

The analgesic and anti-inflammatory properties of salicylic acid derivatives result primarily from the inhibition of cyclo-oxygenase enzymes at the tissue sites. The compounds have potent antipyretic activity too.

Kinetics. The elimination half-life of aspirin (ASA) after oral administration of 600 mg was 0.8 ± 0.31 h and the half life of salicylic acid (SA) was 3.62 ± 0.96 h [88]. The pharmacokinetic parameters of SA after oral administration of 1200 mg ASA to patients with rheumatoid arthritis were: elimination half-life 5.4 ± 0.8 h, apparent volume of distribution 11.0 ± 0.5 l and plasma clearance 25.8 ± 2.0 ml min^{-1} [89].

Therapeutic uses. In pain situations requiring enhanced analgesia codeine or other similar centrally acting opioid drugs are combined with aspirin or paracetamol [90]. Other combinations using phenyltoloxamine, promethazine, phenobarbitone or meprobamate have never been demonstrated to be more effective than the traditionally used opioid combinations. Meprobamate appeared to have a paradoxical algesic effect [91].

Dosage. The analgesic effect of 600 mg oral aspirin occurs within 1 h and last about 5 h. The analgesic dose is 650–1300 mg. Taking multiple dosages in excess of 1300 mg per dose could result in unwanted toxicities. The therapeutic level of aspirin in rheumatoid arthritis is about 150 μg ml^{-1} which can be reached by administration of 4.8 g daily [89]. Analytical methods for the determination of ASA and SA are HPLC [92–94], GLC [95] and fluorimetry [96, 97]. The sensitivities of the HPLC methods are 10 μg ml^{-1} [93] and 0.1 μg ml^{-1} [94].

Diflunisal

Diflunisal is a salicylic acid derivative with analgesic and anti-inflammatory activity.

Kinetics. The drug is well absorbed after oral administration. Peak plasma concentrations are attained within 2 h. Urinary recovery studies indicate that oral bioavailability of the drug is complete. The drug is highly bound to plasma proteins in normal

subjects (>99%) [98]. The elimination of diflunisal depends on conjugation with glucuronic acid. The terminal half-life in plasma ranges from about 5 h following a single 50 mg dose to 15 h following a single 1 g dose [99]. The half-life is prolonged by renal insufficiency [98].

Side effects and dosage. The general spectrum of side effects is similar to that of aspirin, but diflunisal appears to have a more favourable profile. In contrast to aspirin, diflunisal reversibly inhibits platelet aggregation, and it also appears to be less irritating to the gastrointestinal tract [100]. The recommended oral dosage of diflunisal is 500 mg twice a day; thus steady state concentrations are reached in 7–9 days.

Analytical methods based on HPLC [101, 102], with a sensitivity of 5 $\mu g\ ml^{-1}$ and 1 $\mu g\ ml^{-1}$ respectively, have been described.

Para-aminophenol Derivatives

Phenacetin and paracetamol

Phenacetin and its active metabolite paracetamol have analgesic and antipyretic effects that do not differ from those of aspirin. However, they have only weak anti-inflammatory effects.

Kinetics. Oral absorption of phenacetin is markedly influenced by the size of the particles in the preparation. The peak concentration of phenacetin in plasma usually occurs in about 1 h, but extensive 'first-pass' metabolism of the drug occurs after oral ingestion of the usual doses. Phenacetin is metabolized primarily by the liver and is converted to at least a dozen metabolites. In normal individuals 75–80% of the administered dose of phenacetin is rapidly metabolized to paracetamol. Less than 1% of phenacetin is excreted in the urine [103]. The mean half-life of phenacetin is 57.3 ± 3.6 min, the apparent volume of distribution is 217.4 ± 88.8 l and plasma clearance is 2332.1 ± 858.4 ml min^{-1} [104].

Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. The plasma concentration reaches a peak in 30–60 min. Binding of the drug to plasma proteins is variable from 20 to 50%. Following therapeutic doses the drug is excreted in the urine as conjugates: small amounts of hydroxylated and deacetylated metabolites have also been detected [103].

Paracetamol is rapidly absorbed after oral administration but because of its first pass metabolism only 60–90% of the oral dose reaches the systemic circulation. Paracetamol is extensively metabolized, only 2–5% of the dose is excreted unchanged in the urine. Its elimination half-life is 2.3 h and the total body clearance values are about 5 ml min^{-1} kg^{-1} [105].

The elimination half-life of paracetamol after single intravenous doses averaged 2.7 h (range 1.9–4.3) and was not related to age or sex. Volume of distribution was larger in men than in women (0.99 and 0.86 l kg^{-1}) and declined with age. Plasma clearance was 348 ml min^{-1} (between 230 and 502 ml min^{-1}) and also declined with age [106]. Similar values of pharmacokinetic parameters had been reported previously [114].

Therapeutic uses. A significant analgesic effect is only noted after 1.5 h after intravenous administration of 1000 mg acetaminophen. It may exert its analgesic effect by prostaglandin synthetase inhibition: the analgesia thus produced may be time

dependent. Over a 4 h investigation there was no clear relationship between analgesia and acetaminophen concentrations in either central or peripheral compartments [107].

Dosage. The conventional oral dosage of acetaminophen is 325–650 mg every 4 h for adults. For young children the single dose is 60–120 mg depending on weight and age: total daily dosage should not exceed 1.2 g. In therapeutic doses it is a very safe analgesic, but in overdosage may cause severe hepatic necrosis [108]. The average single dose of phenacetin for adults is 300 mg. The total daily dose should not exceed 2.4 g. Paracetamol has somewhat less overall toxicity and is preferred over phenacetin. Paracetamol can be measured in human plasma by GLC, TLC, HPLC, and colorimetric and spectrophotometric methods [109–113].

Antipyrine

Antipyrine is a widely used antipyretic–analgetic pyrazolone derivative.

Kinetics. Antipyrine is well and rapidly absorbed from the gastrointestinal tract. Peak plasma concentration can be reached within 1–2 h. The apparent volume of distribution of antipyrine is 55 l [114]. Since this represents 64% of body weight the data are consistent with reports that antipyrine distributes in total body water [115]. Antipyrine does not bind to plasma and tissue protein and its elimination is totally dependent on its metabolism by the liver. It is excreted in urine entirely as conjugated metabolites [116]. The elimination half-life of the drug is 12.9 h [114], and in another study 12.7 ± 0.8 h [117]. The apparent volume of distribution was determined as 63 ± 4.1 l, and the metabolic clearance of the drug is 62.0 ± 4.0 ml min^{-1} [117]. Antipyrine can be measured in human plasma by GLC [118, 119] and TLC [114].

Indomethacin

Indomethacin has prominent antiinflammatory, analgesic and antipyretic properties similar to salicylates.

Kinetics. The elimination half-life after intravenous single and multiple doses of 25 mg, 25, 50 and 100 mg oral doses, 100 mg rectal and 25 mg three times daily administration of indomethacin ranged between 2.6 and 11.2 h. The apparent volume of distribution ranged from 0.34 to 1.57 l kg^{-1} and the plasma clearance from 0.044 to 0.109 l kg^{-1} h^{-1}. The bioavailability was 98% [120]. The protein binding of indomethacin in human plasma was calculated to be about 90%. The plasma levels in patients receiving continuous treatment (3 25 mg doses daily) were between 0.5 and 3.0 μg ml^{-1} during the 4–5 h immediately after the last dose [121]. Indomethacin is extensively metabolized in the liver. Its main metabolites are *O*-desmethyl indomethacin, *N*-deschlorobenzoyl-indomethacin and *O*-desmethyl-*N*-deschlorbenzoyl indomethacin.

After oral administration indomethacin was rapidly and well absorbed. Maximum plasma concentration (2–3 μg ml^{-1}) was reached after 1–2 h. The elimination half-life was between 5 and 10 h, plasma clearance ranged from 1 to 2.5 ml min^{-1} kg^{-1} [122, 123].

Dosage. The effective plasma concentration of indomethacin is 0.5–3.0 μg ml^{-1}, which can be reached with the dosage of 3 × 25 mg daily. Because of the high incidence and severity of side effects associated with chronic administration, indomethacin must not be routinely used as an analgesic or antipyretic. Indomethacin can be measured in

human plasma by GC–MS [124], fluorimetry [120], HPLC [125–127] and GLC [128–130]. The GC–MS method has a sensitivity of 10 ng ml^{-1}. The sensitivities of the HPLC methods are 0.1 μg ml^{-1} [126], 1.5 ng ml^{-1} [127] and that of the GLC method is 10 ng ml^{-1} [129].

Zomepirac

Zomepirac sodium is a potent, non-narcotic analgesic.

Kinetics. Zomepirac absorption is rapid, peak plasma concentrations being reached within 1–2 h. The elimination half-life was 4.3 h, total body clearance was 184 ml min^{-1} and the volume of distribution was 25.1 l. Because of the lack of kinetic studies, the absolute bioavailability of zomepirac cannot be determined. Comparative i.v. and oral data in rhesus monkeys have shown equivalent bioavailability of zomepirac from the two routes of administration, indicating complete oral absorption [131]. *In vitro* protein binding studies have shown that zomepirac is extensively bound (98.5%) to human plasma proteins.

After a single dose (25 mg) of ^{14}C zomepirac, urinary excretion of total radioactivity amounted to 95% of the dose in 96 h: Free zomepirac was 21.8% of the excreted material. Fecal excretion accounted for about 1% of the administered dose [132]. Human plasma samples can be analyzed for zomepirac concentrations by HPLC [133].

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