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MiniReview

Pharmacokinetic–Pharmacodynamic Modelling of Opioids in Healthy Human Volunteers. A MiniReview

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Abstract: Pain is characterized by its multi-dimensional nature, explaining in part why the pharmacokinetic/pharmacodynamic (PK/PD) relationships are not straightforward for analgesics. The first part of this MiniReview gives an overview of PK, PD and PK/PD models, as well as of population approach used in analgesic studies. The second part updates the state-of-the-art in the PK/PD relationship of opioids, focusing on data obtained on experimental human pain models, a useful tool to characterize the PD of analgesics. For the so-called weak opioids such as codeine, experimental human studies showed that analgesia relies mainly upon biotransformation into morphine. However, the time-course of plasma concentrations of morphine did not always reflect the time-course of effects, the major site of action being the central nervous system. For tramadol, a correlation has been observed between the analgesic response and the PK of the (+)R-O-demethyl-tramadol metabolite. For 'stronger' opioids such as oxycodone, studies assessing the PK/PD of oxycodone suggested that active metabolite oxymorphone also strongly contributes to the analgesia and that analgesia may also be partially related through an action to peripherally located κ-opioid receptors. Different models have been proposed to describe the time-course of buprenorphine. An effect-compartment model was adopted to describe the PK/PD of morphine and its active metabolite, morphine-6-glucuronide (M6G). A longer blood-effect site equilibration half-life $t_{1/2}k_{e0}$ was observed for M6G, suggesting a longer onset of action. The studies assessing the PK/PD of fentanyl and its derivatives showed a short $t_{1/2}k_{e0}$ for analgesia, between 0.2 and 9 min., reflecting a short onset of effect. In conclusion, depending on the speed of transfer between the plasma and the effect site as well as the participation of active metabolites, the time-course of the analgesic effects can be close to the plasma concentrations (alfentanil and derivates) or observed with a prolonged delay (codeine, buprenorphine, morphine). These PK/PD data can be used to better characterize the differences between opioids, and partly explain the important observed variability among opioids in experimental conditions and should be systematically evaluated during drug development to better predict their selection in specific clinical conditions.

Evaluating the effects of analgesic drugs is a complex task. Pain is characterized by its multi-dimensional nature; a number of confounding factors, such as psychological, physiopathological and genetic factors contribute to the large observed intra- and interindividual variability. These issues partially explain why the pharmacokinetic/pharmacodynamic (PK/PD) relationships are not straightforward for the majority of analgesic drugs.

In the first part of this MiniReview, we provide a general idea on pharmacokinetics (PK) and pharmacodynamics (PD), including population analysis. An extensive description of the principles of PK/PD modelling and its application in drug development is beyond the scope of this Mini Review, and extensive reviews have appeared previously [1–6].

The second part summarizes and updates the state-of-the-art in the PK/PD relationship of analgesics [7,8], focusing on data obtained with opioids on experimental human pain models.

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Methods

We searched the relevant literature published from 1966 until April 2011 using the MEDLINE database of the US National Library of Medicine, using the keywords 'pharmacokinetic pharmacodynamic' combined with the terms 'analgesics', 'experimental pain' and 'human'. The analgesics included 'opioids'. However, studies performed after a non-systemic drug administration (intrathecal, epidural, cutaneous) were excluded. Additionally, all other relevant articles were identified using the 'related articles' function.

Results and Discussion

Pharmacokinetics, pharmacodynamics.

Definitions. Pharmacokinetics is the study of the mechanisms of drug absorption, distribution and elimination, and of the kinetics of these processes [9]. Pharmacodynamics (PD) is the study of the biological effects of drugs and their mechanism of action [10]. PK/PD modelling builds the bridge between these two disciplines, linking the

change in concentration over time to the relationship between the concentration at the effect site and the intensity of the observed response [11].

The role of PK/PD modelling in drug development. Pharmacokinetic/pharmacodynamic modelling gives information about the relationship between drug exposure and response. This information can be used to streamline early-phases of the drug development process and dose optimization [1]. In preclinical phase, PK/PD modelling allows an estimation of the potency and intrinsic activity of drugs and can therefore be used to predict dosing regimen for phase I studies [1] and effective and toxic drug concentrations for the clinical development phases [11]. The principal limitations to preclinical PK/PD are the interspecies differences between animals and human beings, making extrapolation more difficult [12]. The application of PK/PD to phase I studies can provide useful information about the dose–concentration effect, either as pharmacological or as toxicological effect, in healthy human volunteers [1] and can be useful to optimize subsequent clinical development phases (i.e. dosing regimens) [11].

Pharmacokinetic models. The aim of PK studies is to establish the relationship between the dose, the dosage form and the plasma concentrations to obtain information on the drug absorption and disposition. These studies rely on the measurement of the drug and/or its active metabolite(s) in an accessible biological fluid (blood, plasma, urine) [1]. The most extensively used PK models are the compartmental PK models. The compartmental models are composed of a central compartment and eventually one or more peripheral compartments [12]. The body is represented as a system of compartments, which does not have any anatomical meaning [13]. The one-compartment model, which represents the body as a single compartment, is applicable to drugs that rapidly distribute through the body. The plasma concentration C is given by the following equation [10]:

$$C = C_0 \cdot k^{-k \cdot t} \tag{1}$$

where C_0 is the concentration at time zero, t is the time and k is the elimination rate constant. In the multi-compartment models, the compartments are represented by tissues that equilibrate more slowly, which are poorly perfused or surrounded by protective membranes [10].

Pharmacodynamic models. When linked to PK, PD makes the drug concentration profile derived from the PK analysis pharmacologically relevant by completing the link between the dose and the effect [4]. PK/PD models predict the drug effects from drug concentrations at the active site in the steady-state [5]. In the simplest form, the observed effect is directly related to the effect-site concentrations. In addition, it is assumed that these concentrations are in equilibrium with the plasma concentrations. This is the case for all direct and reversibly acting drugs under the PK steady-state conditions [11]. The basic PD models include the linear effect concentration model, the log-linear effect concentration model and the simple E_{max} model (hyperbolic) that are described by Equations 2, 3 and 4, respectively. However, the classic and most extensively PD model is the sigmoid E_{max} model, as described by the Equation 5 [5,10,11].

$$E = E_0 + S \cdot C \quad \text{(linear model)} \tag{2}$$

where E is the pharmacological effect, E_0 is the effect baseline value, S is the slope parameter and C is the concentration. This is the simplest PD model, which predicts that effects are directly proportional to the concentrations at the active site. However, this model cannot predict a maximum effect.

$$E = m \cdot \ln(C + C_0) \quad \text{(log-linear model)} \tag{3}$$

where m is the slope of the apparently linear segment of the curve. In the above-mentioned model, the relationship between the log-concentration and the effect appears linear within a certain effect range, often between 20% and 80% of the maximal effect. Therefore, this model is only applicable to 60% of the range of observations arising from biologically based concentration–effect models.

$$E = \frac{E_{max} \cdot C}{EC_{50} + C} \quad (E_{max} \text{ model}) \tag{4}$$

where E_{max} is the maximal effect and EC_{50} is the concentration needed to achieve 50% of the maximal effect, expressing the potency of the ligand. This model derives from theoretical considerations on drug-receptor interaction. The advantage of this model is that it predicts a maximum effect.

It is possible to modify the steepness or curvature of the response–concentration curve by the addition of a parameter γ to the ordinary E_{max} model. This model is referred to as the sigmoid E_{max} model. The γ parameter is called the Hill coefficient. If γ equals to 1, the model is hyperbolic (simple E_{max} model). It is observed that the steeper the value of γ, the more curvature (steeper) is the line around the EC_{50} value. As compared with the simple E_{max} model, the addition of the parameter γ allows to more conveniently fit different types of experimental data. However, it increases the number of parameters to estimate, therefore decreasing their precision for a given set of data.

$$E = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \quad (\text{sigmoid } E_{max} \text{ model}) \tag{5}$$

Typical PD models, such as the E_{max} model, may also be used to describe an excitatory or an inhibitory effect.

PK/PD models. Integrated PK/PD models describe the relationship between the plasma and/or tissue drug concentrations and a pharmacological effect. The PK/PD models can be classified on the basis of how the PK and PD data are related to each other. Some outcome variables, such as pain to assess analgesia, psychometric depression or anxiety measures to assess antidepressants and antipsychotics, are highly subjective but validated by quantitative scales. Thus, precise PD evaluation becomes challenging [4].

Direct versus *indirect link model.* In the direct link models, the plasma concentrations are directly linked to the effect-site concentrations. The ratio between both the concentrations is constant as equilibrium is assumed to be rapidly achieved. Hence, the measured concentration in plasma can directly serve as an input function in the PD model component, thereby directly linking measured concentration to the observed effect. Concentration and effect maxima would then occur at the same time. In the indirect link models, a temporal dissociation is observed between the time-courses of concentration and effect, which results in a hysteresis in the concentration–effect relationship [1,11]. When the data points (concentration response measurements made at varying times after a dose) are connected in a chronological order, the way they appear to turn defines the hysteresis loop as 'anticlockwise' or as 'clockwise'. The arrows show the direction of time after the dose (fig. 1). In fig. 1, the direction of time is anticlockwise. The effect for a given plasma concentration is initially low, but increases as the drug is distributed out of the plasma to the site of action. It suggests that there is a delay in the kinetics of effects when compared with the kinetics of the plasma concentration. The PD effects increase more slowly, reach a peak later and are more sustained than plasma concentrations. This can be suggestive of: a deep tissue site (i.e. central nervous system, CNS), the transformation of a prodrug into an active metabolite or an indirect mechanism of pharmacological action. A clockwise hysteresis loop occurs when the effect decreases quicker than plasma concentration. This is suggestive of the development of tolerance to the drug [5,14].

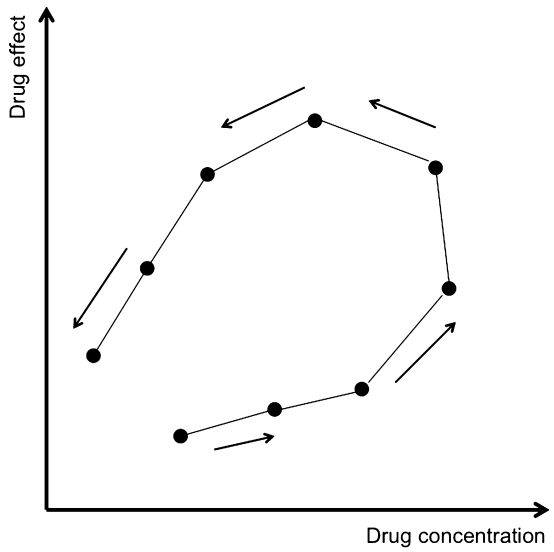

Fig. 1. Anticlockwise hysteresis loop. The effect for a given plasma concentration is initially low, but increases as the drug is distributed out of the plasma to the site of action, which suggests a delay in the kinetics of effects when compared with the kinetics of the plasma concentration.

The concept of the effect-compartment model has been proposed as a general approach for the indirect link models. The time-course of the effect itself can be used to assess the changes in concentration at the effect site [11]. A hypothetical effect-compartment is defined so that the kinetics of the drug in this compartment is parallel to the kinetics of the pharmacological effect. The equilibration process between the plasma and the effect site is determined by the first-order rate constant k_{e0}. This describes the dissipation of the drug from the above-mentioned effect-compartment. Thus, the kinetics of the concentrations in the effect-compartment can be expressed as a function of the parameters of the PK model and k_{e0} [5].

Direct versus *indirect response model.* After dosing, there is a build-up of the drug response governed by various inhibitory and/or stimulatory factors. In the direct response model, the drug affects the response without any delay other than the time needed for the drug to reach the sampled compartment. In this case, the involved transduction and response mechanisms mediate the effect rapidly. The indirect response model is used when a temporal dissociation between the time-courses of concentration and effect is observed, the drug acting on build-up or loss of response. This model is characterized by either the inhibition or the stimulation of a physiological process responsible for the synthesis or degradation of an endogenous substance or response mediator. Examples of indirect response models include the anticoagulant effect of vitamin K antagonists or the antipyretic effect of NSAIDs. These models are more complex to implement but may be more appropriate than the effect-compartment model if one suspects a physiological origin to the delay between the kinetics of concentration and the effects [1,5,10,11,15]. Indirect response models are popular because they provide a reasonable description of the mechanism of action for many drugs [6].

Time-variant versus *time-invariant models.* In time-invariant models, the intensity of the effect is secondary to the measured concentration. Therefore, the PD parameters remain constant over time. The time-invariant models apply to most drugs. However, some drugs display time-dependent changes of their PD parameters such as E_{max} and EC_{50}, which is observed as changes in effect intensities without changes in drug concentrations at the effect site. The respective models are categorized as time-variant. The decrease or increase in sensitivity is referred to respectively as tolerance or sensitization [1,11]. Tolerance phenomena may occur as a result of down-regulation of receptors, or depletion of co-factors, precursors, endogenous compounds or messengers.

Population approach. An important problem in drug therapy is the variability of response among individuals in a population, which can manifest itself both in the PK and in the PD. Numerous studies have demonstrated a contribution of kinetic and dynamic variabilities to the overall variability in clinical response [3]. The population approach is a model-based method of analysing observations in individuals that accounts for and describes how individuals differ from each other, as well as the behaviour of the population [16]. This approach aims at modelling the concentration–effect relationship through a limited number of measurements per patient and allows to study the influence of co-variables such as age and gender on PD parameters, therefore to better model inter- and intra-individual variability [5]. It is commonly used to characterize how typical differences between individuals influence dosage requirements. In clinical studies, there are often data available from many individuals but not many data points from specific individuals, because of practical or ethical issues. Such data are referred to as sparse data [16]. Non-linear mixed effects modelling was introduced in the late 1970s to study and analyse sparse data [17]. Population analysis involves the use of combined data from several individuals to estimate the PK and/or PD parameters of the population. It also provides estimates of the variability of these estimates among individuals [16]. The potential benefit of an accurate population-based PK and PD model is that it can be used to optimize the prediction of individual dose requirements [18]. There are three approaches for determining population PK and PD model parameters: the two stages, the pooled and the mixed effects approaches, which are described elsewhere in more detail [6]. The standard approach is the two-stage approach where PK data are derived for every individual in the population and then the population mean is calculated to depict the population and its variability. It is only possible with enough data to estimate the model parameters for each individual, and if all data from each individual are described by the same structural model. The pooled approach involves pooling the data from all individuals to obtain an estimation of the population parameters. However, this method is generally not valid for the analysis of PD data. The last approach, the non-linear mixed effects model has been described as the most satisfying for repeated measurements. The data for all individuals are analysed simultaneously, but mixed models take into account both fixed and random effects [6,18]. A data model is a mathematical expression that describes an observation in terms of two parts, explained and unexplained. The explained part is usually a function of certain constants, called parameters, and known covariates, called independent variables. The unexplained part is usually treated as random. Parameters include PK parameters (bioavailability, clearance etc.) and PD parameters (E_{max}, ED_{50} etc.). The independent variables include dose, time since dose, patient age, weight, sex, severity and presence of diseases [19]. Mixed effects models have been described for continuous measures of drug effect, including both direct and indirect PD models. Random effects models have also been described for categorical response data and survival-type data [6]. The model derived by Mandema and Stanski [20] characterizing ketorolac analgesia illustrates the complexity of analysing analgesic drug trials. The authors used population models (with random effects) to deal with repeated measurements, non-continuous responses and non-random censoring (remedication).

PK/PD relationships in the field of analgesic drugs. Pain is an unpleasant, multi-dimensional sensory and emotional experience that cannot be described by a single parameter [21]. A majority of human studies assess pain in a subjective manner using categorical and visual analogue scales [22]. Different methods in human experimental pain research exist to quantitatively assess the various aspects of pain [21]. These methods constitute a useful tool to characterize the analgesic effects of drugs [23]. The advantages of experimental pain include the control of the intensity, duration and modality of the stimulus as well as a quantitative assessment of the responses [24]. The methods for assessing experimental pain in man [21,24] and the

PK/PD of anaesthetic drugs, focusing on anaesthesiological PD end-points [18,25–27] have been reviewed elsewhere. The present MiniReview focuses on analgesia.

Opioids differ with respect to the correlation between the plasma concentrations and the effects. For some opioids, there appears to be a delay between the time-course of the plasma concentrations and the time-course of the effects [8]. In some cases, the metabolites may contribute to analgesia. Thus, the relationship between the plasma concentrations and the analgesic effects becomes more complex. Depending on the speed of transfer between the plasma and the effect site, the time-course of the analgesic effects can be close to the plasma concentrations, or delayed. The delay would be longer if the transfer is slower. This rule governs the onset and offset of the opioid effects. For an opioid with a fast transfer and a rapid dissociation curve from the opioid receptors, such as alfentanil, the effect would start shortly after the drug administration and disappear as soon as the plasma concentrations decrease. Such a profile can be interesting in the setting of ambulatory surgery. Alternatively, a slow transfer between the plasma and the effect site prolongs the clinical effects of opioids, such as morphine. Such a kinetic profile can be interesting for chronic pain and long-term therapy [8].

'*Weak*' *opioids. Codeine.* Codeine analgesia relies upon biotransformation into morphine, its presumed active moiety. *In vitro* release of morphine occurs when codeine is incubated with liver microsomes of various species, including the rat [28]. The O-demethylation of codeine to morphine has been described to occur *in vivo* in man in the 1950s [29]. About 10% of an oral dose of codeine is converted into morphine by the cytochrome P450 (CYP) 2D6. Desmeules *et al.* [30] showed that no analgesic effect on the nociceptive flexion reflex (NFR) could be detected when the production of morphine was abolished by quinidine, a inhibitor of CYP2D6, as well as in a poor metabolizer of CYP2D6. No modelling of the data was performed. However, the authors showed latency between the peak plasma morphine (1 hr after codeine administration) and the apparent maximal effect of codeine (2 hr), which probably relies upon the fact that the major sites of action of morphine and its active metabolite morphine-6-glucuronide are located within the CNS. The group of Sindrup *et al.* confirmed that the analgesic effect of codeine depends on the genetic polymorphic transformation of codeine to morphine by three studies on experimental human pain models [31–33]. Again, no modelling of the data was performed, but the authors observed a significant correlation between the plasma concentration of produced morphine in extensive metabolizers of CYP2D6 and analgesic effects of administered codeine [31]. Their results also suggest that local conversion of codeine to morphine in the CNS may be of major importance for codeine analgesia and that the plasma concentrations of morphine may not reflect the concentrations at the site of action and may therefore be irrelevant for the analgesic effect of codeine [32,33]. Other authors such as Suri *et al.* [34] reported the analgesic effect of codeine on experimental human pain models; however, PK/PD correlation was not be performed as plasma concentrations were not measured.

Tramadol. Enggaard *et al.* [35] aimed at correlating the analgesic effect of tramadol to the plasma concentrations of tramadol and its active metabolite (+)R-O-demethyl-tramadol [(+)-M1 metabolite], responsible for the opioid effects and produced via CYP2D6. They compared 10 extensive metabolizers to 10 poor metabolizers of CYP2D6. Pain detection, pain tolerance and the pain summation thresholds to percutaneous electrical stimulation of the sural nerve, as well as the tolerance to the cold pressor test were used to evaluate the analgesic effects. No modelling of the data was performed. However, the relationship between response and drug levels (each enantiomer of tramadol and of the M1 metabolite) was tested with the Spearman rank correlation test. No significant correlation was observed between the responses and the corresponding area under the concentration time curve from 0 to 90 min. ($AUC_{0–90}$) of tramadol. However, a positive correlation was observed between the reduction in peak pain intensity during the cold pressor test and the corresponding $AUC_{0–90}$ of (+)-M1 in extensive metabolizers. Filitz *et al.* [36] assessed the PK/PD relationship of tramadol and its combination with paracetamol in a human pain model of electrically evoked pain and secondary hyperalgesia. A sigmoid model was used for PD modelling and the delay between the increase in the plasma concentration and the onset of the effect was modelled by an effect compartment. The effect-site concentration of tramadol was derived from the plasma concentration of the (+)-M1 metabolite, which was calculated using the pharmacokinetic data for the tramadol enantiomers and their metabolites from previously published data. It was observed that the predicted maximum concentration of the active metabolite was markedly delayed compared to the predicted concentration of the parent drug. Therefore, it was unnecessary to assume an additional effect-compartment for the active metabolite to model the hysteresis between dosing and effect. Thus, the effect-site concentration of tramadol was just the predicted plasma concentration of the active metabolite and therefore no estimate was given for k_{e0} of tramadol. Single drugs produced slight decreases in pain ratings, and this effect tended to be reinforced by the combination, although the difference between the treatment groups was not significant. Paracetamol alone and combined with tramadol produced significant reduction in hyperalgesic areas whereas tramadol alone had no effect. Only marginal analgesic and antihyperalgesic effects of tramadol and its metabolites were detected in the model used in this study, which made results analysis difficult and seems to be contradictory to the clinical experience with tramadol. As discussed by the authors, this could be due to the complex mechanisms of action of tramadol on serotoninergic descending inhibitory systems which may be difficult to detect by the model used in the study. The authors also used the data from PD modelling to determine the type of interaction between paracetamol and tramadol using the isobole technique. This technique showed that for the combination, lower doses were required to achieve the maximum effect predicted by the PD model, thus indicating a supra-additive interaction between paracetamol and tramadol, on both analgesic and antihyperalgesic effects.

'*Strong*' *opioids. Oxycodone.* A study of Staahl *et al.* [37] compared the PK/PD relationship of morphine and oxycodone in a multimodal experimental pain model. Here, a linear concentration–effect relationship with an effect-compartment link was observed with respect to oxycodone for somatic pain (skin). The $t_{1/2}k_{e0}$ for somatic pain was 12 and 22 min. for thermal and electrical-induced pain, respectively. For visceral pain, the data showed a obvious relationship between the pain threshold and the plasma concentrations with no delay. Thus, a blood compartment link model could be applied. The obtained results suggest that when compared with morphine, oxycodone works at a peripherally located receptor, which could be the κ-opioid receptor. The initial peripheral analgesic effect of oxycodone was confirmed by another study [38]. This study in healthy human volunteers showed a linear relationship between the plasma concentrations of oxycodone and the analgesic effect with no effect delay, on the different pain stimuli, such as cutaneous thermal pain, muscular pain and visceral pain. A recent study assessed the effect of CYP2D6 genetic polymorphism and CYP2D6- and CYP3A4-mediated drug–drug interaction on the PD of oxycodone in healthy volunteers [39]. The PK/PD relationship was assessed using the Spearman correlations. A positive correlation was observed between the area under the drug effect–time curve for the objective and subjective pain thresholds assessed by the NFR and the oxymorphone and noroxymorphone areas under the concentration curve (AUC). However, no correlation with oxycodone and noroxycodone PK was demonstrated. These results suggest that the metabolites oxymorphone and noroxymorphone strongly contribute to oxycodone-related analgesia. Other studies performed in healthy human volunteers showed a role for CYP2D6 on the PD of oxycodone, although not assessing PK/PD relationship [40,41].

Buprenorphine. Several PK/PD models have been proposed to describe the time-course of the effects of buprenorphine [42–45]. The

analgesic and antihyperalgesic effects of buprenorphine, a partial opioid-receptor agonist, were compared after the IV (0.15 mg) and sublingual (0.2 mg) administration in 15 healthy volunteers. A cross-over study was performed [42]. Intradermal electrical stimulation was used to induce ongoing pain and secondary hyperalgesia to the punctuated stimulation. The analgesic and antihyperalgesic effects after the sublingual administration were delayed by 15.8 min. when compared with the IV administration. A sigmoid model with an effect-compartment link was used to model the data. Buprenorphine-induced analgesia decreased slightly at the end of the observation period (180 min.). However, an antihyperalgesic effect was still present. A significantly longer equilibration half-life $t_{1/2}k_{e0}$ was estimated for antihyperalgesia when compared with analgesia (288 *versus* 171 min.). Moreover, the EC_{50} and the shape parameter γ were significantly higher for the analgesic effects when compared with the antihyperalgesic effects (0.30 *versus* 0.11 ng/ml and 3.2 *versus* 1.9, respectively). The resulting data suggest that the concentration–effect relationships are distinct for analgesia and antihyperalgesia. Yassen *et al.* [43] proposed a combined biophase equilibration/receptor binding model to best describe the time-course of the antinociceptive effect. The estimated half-life of biophase equilibration ($t_{1/2}k_{e0}$ = 155 min.) was in the same range as reported by Koppert *et al.* [42] for buprenorphine-induced analgesia (171 min.). The proposed model suggests that the rate of onset and offset of the antinociceptive effect is predominantly determined by the distribution of buprenorphine to the effect site. This was because the half-life of the receptor dissociation value was short (8.8 min.). Conversely, another study proposed a linear direct effect model to best describe the effect of transdermally applied buprenorphine on bone-associated pain, heat pain and cold pressor pain [44]. A cross-over study in 12 healthy volunteers assessed the time-course of buprenorphine effects on different pain models (thermal pain, NFR, cold pressor test). The maximum effect on the NFR was observed at 120 min. and the maximum effect on cold pain tolerance was observed at 30 min. The changes in values compared with baseline remained statistically significant for 120–240 min. after drug administration, hence across a wide range of concentrations during the elimination phase. The most likely explanation for this finding is the high affinity of buprenorphine at μ-opioid receptors [45].

Morphine. Morphine is an opioid analgesic with several therapeutic applications, including postoperative and cancer pain. Morphine undergoes glucuronidation in two metabolites, namely morphine-3-glucuronide (M3G, approximately 50% of an IV dose) and morphine-6-glucuronide (M6G, about 10%). M3G does not display any analgesic effect. However, M6G may contribute to morphine-induced analgesia [46]. Several studies have attempted to assess the PK and PD of morphine and M6G in healthy human volunteers [37,46–49]. The analgesic effects of morphine and M6G as well as the PK/PD relationship were evaluated in a cross-over study assessing thermal pain in 12 healthy volunteers. These volunteers received a 10-mg 5-min. morphine intravenous infusion [46]. The fractional contribution of M6G to analgesia ranged from 0.1% to 66%. The above-mentioned contribution appeared to differ between men and women. A mean contribution of 32 ± 19% (mean ± S.E.M.) in men (n = 3) and 13 ± 8% in women was observed. As the overall response to morphine increased, the fractional contribution of M6G to analgesia declined. An indirect response effect-compartment model was used, which assumed a linear relationship between the thermal pain threshold and the effect-site concentration. The mean k_{e0} value was 4.43/hr. The sex difference in morphine analgesia has also been observed in another study [48]. This study was performed in 10 healthy male and 10 healthy female volunteers. These volunteers were administered a 100 μg/kg IV bolus of morphine followed by a 1-hr 30 μg/kg/hr infusion. The pain detection and tolerance thresholds to a transcutaneous electrical stimulation were used to assess the antinociceptive effect of morphine. An effect-compartment model was postulated. A significant difference between the men and women was observed for the parameters k_{e0} and AC_{50}. This is the effect-site concentration causing 50% attenuation in an inhibitory sigmoid E_{max} model. The $t_{1/2}k_{e0}$ was 1.6 and 3.8 hr for pain detection threshold, and 1.6 and 4.8 hr for the pain tolerance threshold in men and women, respectively. The concentrations of AC_{50} were 71.2 and 41.7 nM for the pain detection threshold in men and women, respectively. The concentrations of AC_{50} were 76.5 and 32.9 nM for pain tolerance threshold in men and women, respectively. The observed sex differences in effect were unrelated to pharmacokinetic differences. The results suggested that morphine had a greater potency but showed a slower speed of onset and offset of analgesia in women. This difference does not appear because of the metabolite M6G, as shown by a study performed by the same research group, which used the same experimental transcutaneous model of pain [47]. In this cross-over, placebo-controlled study, 10 healthy male and healthy female volunteers received either M6G (0.3 mg/kg) or placebo. M6G produced a greater analgesia than placebo. However, a sex-dependent effect could not be detected. A large inter-individual variability as expressed by the coefficient of variation (CV) was observed for $t_{1/2}k_{e0}$ (CV = 218%) and C_{25} (CV = 167%), which is the effect-site M6G concentration causing a 25% increase in current for pain tolerance. The $t_{1/2}k_{e0}$ was 6.2 hr, thereby suggesting a long delay between the time-course of plasma concentration and the time-course of analgesic effects. The above-mentioned delay could be explained by a slower penetration of the blood–brain barrier by M6G when compared with morphine, which could be due to its more hydrophilic nature or its interaction with some transporters. Skarke *et al.* [49] further confirmed this difference of delay between morphine and M6G. In the study conducted by Skarke *et al.*, 12 healthy volunteers received morphine (26–66 mg), M6G (63–112 mg) or placebo as an IV bolus, in a cross-over design. This was followed by infusion during 1.8–6.4 hr. Morphine and M6G significantly increased the pain tolerance to electrical stimulation when compared with placebo, but not the pain detection threshold. No difference was observed between morphine and M6G. The $t_{1/2}k_{e0}$ was 2.6 and 8.2 hr for morphine and M6G, respectively. Pain tolerance was linearly related to the effect-site concentrations. The concentration–effect relationship was flatter for M6G than for morphine, as expressed by a lower value of the slope (0.05% *versus* 0.6% of increase in pain tolerance per nanomolar of opioid at the effect site). In other words, a concentration of 1114 nM of M6G was required to increase the pain tolerance of 50%, as compared with 85 nM of morphine. The above-mentioned observation points toward a lower potency of M6G when compared with morphine *in vivo* [8]. However, this is in disagreement with the previous observations [46]. The amount of M6G required to achieve the analgesic effect when compared with morphine was estimated in the present study [49] to be about 25 times higher than the M6G formed from morphine. Thus, the above-mentioned observation suggests a small contribution of M6G to the observed short-term central opioid effects of morphine in normal conditions. However, with a long-term morphine treatment, it is possible that M6G accumulates and could reach sufficient concentrations to contribute more significantly to the analgesic effects of morphine. Staahl *et al.* [37] compared the PK/PD relationship of morphine and oxycodone in a multimodal experimental pain model, which implied both visceral and somatic experimental pain, measured in the oesophagus and on the skin, respectively. This cross-over study in 24 healthy volunteers (12 men, 12 women) showed a linear concentration–effect relationship for morphine, with an effect-compartment link. The $t_{1/2}k_{e0}$ for somatic pain was 23 and 43 min. for thermal- and electrical-induced pain, respectively. The $t_{1/2}k_{e0}$ for visceral pain was 433 and 24 min. for mechanical and electrical stimulation, respectively. A greater variability was observed for visceral pain, thereby making modelling more difficult. Finally, a study in 16 healthy individuals compared the PK/PD relationship for morphine-induced antinociception and respiratory depression [50]. The respiratory variables measured were the respiration at a fixed end-tidal partial pressure of carbon dioxide of 50 mmHg and the acute hypoxic ventilatory response. These variables were obtained as described in detail elsewhere [50]. The above-mentioned study used pain tolerance to electrical stimulation as an experimental model. The blood-effect site equilibration half-life $t_{1/2}k_{e0}$ did not differ significantly between

analgesia and respiratory depression (4.4 hr). In addition, the potency parameters of analgesia and respiratory depression also did not differ (32 nM). The above-mentioned observation suggests similarities in the central μ-opioid analgesic and respiratory pathways. However, the shape parameter γ from the sigmoid E_{max} model was 2.4 for respiration and one for analgesia. This difference indicates that a mild to moderate respiratory depression tends to occur at morphine concentrations that does not cause any analgesic effect (<10 nM). However, at greater concentrations (10–100 nM), the gain in the analgesic effect (slope) is greater than the occurrence of the respiratory depression.

Fentanyl, remifentanil, alfentanil, sufentanil. A majority of the studies assessing the PK/PD relationship for fentanyl, remifentanil, alfentanil and sufentanil used electroencephalogram-derived parameters instead of analgesia for the PD analysis [8]. A small number of pain studies performed in healthy human volunteers were found [44,51–54]. The first study compared the PK/PD of fentanyl after IV and intranasal administration of a similar dose in 24 patients undergoing a third molar extraction in a cross-over fashion [51]. An absorption lag of 5.2 min. was added to the PK model for intranasal administration. The above-mentioned route resulted in a bioavailability of 89%. The best PK/PD model was a fractional sigmoid E_{max} model with a delay. The blood-effect site equilibration half-life $t_{1/2}k_{e0}$ was very short (2.4 min.). It displayed a large inter-individual variability with a CV of 69%. The concentration–effect relationship was steep, with an EC_{50} of 0.46 ng/ml. A recent study evaluated the effect of transdermal fentanyl on several experimental pain models, such as bone pressure stimulation, heat stimulation, cold pressor test and hyperalgesic pain models [44]. Fentanyl displayed a significant analgesic effect only on the cold pressor test, with a linear direct effect model best describing the data. The lack of delay in the time-course of the PD effect with respect to the time-course of the drug concentration is indicative of a peripheral effect followed by a central effect.

Lötsch and Angst [52] evaluated the effect of remifentanil on freeze-induced hyperalgesia. Each of the 12 healthy individuals received two of the six controlled infusions of remifentanil to target two plasma concentrations between 0 and 6 ng/ml. A power model was used to describe the analgesic effects of remifentanil. This was because the data did not support a sigmoid model. Remifentanil attenuated mechanical hyperalgesia to punctuate stimulation and to blunt pressure in a linear and dose-dependent fashion. The plasma concentration needed to reverse the hyperalgesic effect was estimated to be 5.2 and 1.0 ng/ml after punctuated stimulation and pressure pain, respectively. Remifentanil was about two times as effective in attenuating hyperalgesia to blunt stimulation than to punctuated stimulation. This observation was expressed by a steeper slope characterizing the relationship between the plasma concentration and the reduction in pain. The obtained results confirm the previous observations, which state that hyperalgesia evoked by blunt and punctuated stimuli at the site of injury is distinct forms of mechanical hyperalgesia, mediated by C- and Aδ-fibres, respectively. Thus, these two forms should be distinguished. Gustorff *et al.* [54] evaluated the effect of remifentanil on heat pain thresholds in 20 healthy volunteers. Although no PK/PD model was proposed (the plasma concentrations of remifentanil were not measured), the authors estimated that the dose effective for at least 50% of the volunteers was 0.05 μg/kg/min. Another study used a sigmoid E_{max} model to describe the PK/PD relationship of remifentanil on an experimental model involving pain tolerance to a pressure applied to the tibia and the sternum [55]. This study in 48 healthy volunteers receiving either remifentanil or alfentanil or placebo showed a very short equilibration half-life $t_{1/2}k_{e0}$ of 1.3 min. The choice of the model has been subject to debate, as pain tolerance did not reach a true maximum level. Some authors have suggested that a linear or a power model would have been the better suited model [8]. Egan *et al.* [56] investigated the effect of a remifentanil bolus injection on pressure algometry. They showed that analgesia increased as the dose was increased over to a dose of 25 μg. They also built a population PK model which was then used for PK simulations, showing that frequent small bolus of remifentanil can be expected to produce a concentration *versus* time profile in the site of action that is a reasonable approximation of a steady-state infusion. No PK/PD analysis was performed in this study.

The PK/PD of alfentanil was studied in 36 healthy volunteers, 18 men and 18 women, on transcutaneous electrical pain (16 volunteers), noxious heat (10 volunteers) and sedation (10 volunteers) [53]. The above-mentioned study also aimed to assess the influence of sex on the alfentanil analgesia. The volunteers received alfentanil or placebo as 30-min. infusion in a cross-over design. The infusion rate aimed to target the plasma concentrations of alfentanil of 50 ng/ml from 0 to 10 min., 100 ng/ml from 10 to 20 min. and 150 ng/ml from 20 to 30 min. after the start of the infusion. An inhibitory sigmoid E_{max} model with an effect-compartment was used. In respect of electrical pain, the concentrations of $t_{1/2}k_{e0}$ and AC_{50} were 9 min. and 133 ng/ml, respectively. In respect of thermal pain, the concentrations of $t_{1/2}k_{e0}$ and AC_{50} were 0.2 min. and 141 ng/ml, respectively. No difference was observed between the men and women. The differences in the equilibration half-life between electrical and heat stimulation suggest that these distinct pain models may activate different pain pathways with differences in central processing.

The authors are not aware of high-quality study assessing the PK/PD of sufentanil analgesia.

Conclusion

Owing to the multi-dimensional nature of pain, the PK/PD relationships remain complex for analgesics. Models of experimental pain in healthy human volunteers are useful tools to characterize the analgesic effect of drugs. This is because the intensity, duration and modality of the stimulus can be controlled. However, it is difficult to obtain good data for PK/PD modelling because of the existence of non-responders to the experimental pain model as well as to the analgesic drug. Opioids differ with respect to the correlation between the plasma concentrations and the effects. Moreover, in some cases, active metabolites contribute to analgesia. Thus, the PK/PD relationship becomes more complex (e.g. codeine and morphine, tramadol and the M1 metabolite, morphine and its metabolite morphine-6-glucuronide). Depending on the speed of transfer between the plasma and the effect site, the time-course of the analgesic effects can be close to the plasma concentrations (alfentanil and derivates) or observed with a delay (morphine, buprenorphine). As already observed in 1997 [7], many of the published studies performed PK/PD analysis after the administration of a single dose or after a short infusion. Therefore, additional data after multiple dosing are required, for instance, to assess the role of M6G in morphine-related analgesia. As for morphine, more PK/PD studies evaluating the role of the active metabolites are required.

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