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Pharmacokinetic-Pharmacodynamic Modelling of the Antipyretic Effect of Two Oral Formulations of Ibuprofen

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Abstract

Objective: To analyse the population pharmacokinetic-pharmacodynamic relationships of racemic ibuprofen administered in suspension or as effervescent granules with the aim of exploring the effect of formulation on the relevant pharmacodynamic parameters.

Design: The pharmacokinetic model was developed from a randomised, crossover bioequivalence study of the 2 formulations in healthy adults. The pharmacodynamic model was developed from a randomised, multicentre, single dose efficacy and safety study of the 2 formulations in febrile children.

Patients and participants: Pharmacokinetics were studied in 18 healthy volunteers aged 18 to 45 years, and pharmacodynamics were studied in 103 febrile children aged between 4 and 16 years with bodyweight ≥25kg.

Methods: The pharmacokinetic study consisted of two 1-day study occasions, each separated by a 1-week washout period. On each occasion ibuprofen 400mg was administered orally as suspension or granules. The time course of the antipyretic effect was evaluated in febrile children receiving a single oral dose of 7 mg/kg in suspension or 200 or 400mg as effervescent granules. During the pharmacodynamic analysis, the predicted typical pharmacokinetic profile (based on the pharmacokinetic model previously developed) was used.

Results: The disposition of ibuprofen was described by a 2-compartment model. No statistical differences ($p > 0.05$) were found between the 2 formulations in the distribution and elimination parameters. Absorption of ibuprofen from suspension was adequately described by a first-order process; however, a model with 2 parallel first-order input sites was used for the drug given as effervescent granules, leading to time to reach maximum drug concentration (t_{max}) values of 0.9 and 1.9

hours for suspension and granules, respectively. The time course of the antipyretic effect was best described using an indirect response model. The estimates (with percentage coefficients of variation in parentheses) of E_{max} (maximum inhibition of the zero-order synthesis rate of the factor causing fever), EC_{50} (plasma concentration eliciting half of E_{max}), n (slope parameter) and k_{out} (first order rate constant of degradation) were 0.055 (10), 6.16 (14) mg/L, 2.71 (18) and 1.17 (23) h^{-1}, respectively, where T_0 is the estimate of the basal temperature, 38.8 (1) °C. No significant ($p > 0.05$) covariate effects (including pharmaceutical formulation) were detected in any of the pharmacodynamic parameters.

Conclusions: Because of the indirect nature of the effect exerted by ibuprofen, the implications of differences found in the plasma drug concentration profiles between suspension and effervescent granules are less apparent in the therapeutic response.

The absorption and disposition of many of the nonsteroidal anti-inflammatory drugs (NSAIDs), which are drugs widely used in the treatment of pain, fever and rheumatic and inflammatory diseases, have received considerable attention over the past 3 decades.[1] Several articles have studied the effect of demographics, food or pathophysiological states on the pharmacokinetics of NSAIDs.[2-4] In addition, the impact of using different routes of administration and/or pharmaceutical formulations on the plasma versus time profiles has also been evaluated.[5-7]

In general, disposition parameters (apparent volume of distribution and total plasma clearance) are not (or only slightly) affected by the route or formulation components. However, absorption profiles [usually characterised by C_{max} (maximum concentration of drug in plasma) and t_{max} (time to C_{max})], as expected, are highly dependent on those 2 factors.[5-7] Measurements of t_{max}, C_{max} and other parameters such as area under the curve of plasma drug concentration versus time curve (AUC) are frequently used to determine bioequivalence between different pharmaceutical formulations. Such measurements could also be used to make assumptions regarding the time course of drug effect. For example, higher values of t_{max} and C_{max} could be considered indices of delayed and higher therapeutic (or adverse) effects, respectively.

Taking into account the fact that for most drugs the relationship between exposure and effect is nonlinear and that plasma concentrations cannot usually be related (directly) to drug effect,[8,9] such assumptions need revision. For the particular case of NSAIDs there is evidence for distribution delays to the biophase and/or indirect response mechanisms. Kelley et al.[10] developed a pharmacokinetic-pharmacodynamic model of the antipyretic effect for each of the enantiomers of ibuprofen; the model postulated an effect compartment. On the other hand, an indirect mechanism model to account for the time course of the antipyretic effect of racemic ibuprofen was proposed by Garg and Jusko[11] in 1994. Moreover, the literature contains examples where pharmacodynamic drug properties vary depending on the rate of drug administration (which can be extended, for example, to changes in the rate of absorption).[12] It is therefore of interest to address this issue for the particular case of NSAIDs because of the variety of NSAID formulations that are currently being used in therapeutics.

In the present paper, the plasma drug concentration versus time profiles of racemic ibuprofen given in suspension or as effervescent granules to healthy volunteers were described using an appropriate pharmacokinetic model. A population pharmacodynamic model (using the pharmacokinetic model developed previously) describing the mean and individual antipyretic profiles of 103 children receiving the same formulations as the healthy volunteers was built with the goal of exploring the effect of formulation (used as a covariate in the population model) on the relevant pharmacodynamic

parameters and their estimates of interindividual variability.

Methods

This work includes results from a pharmacokinetic (bioequivalence) study and a pharmacodynamic (efficacy and safety) study.

Pharmacokinetic Study

Participants

18 healthy volunteers participated in the study. All participants gave signed informed written consent, and approval was obtained from the ethics committee of the Infanta Cristina University Hospital, Badajoz, Spain. The study was conducted according to the guidelines in the Declaration of Helsinki. Males (n = 10) and females (n = 8) aged between 18 and 45 (mean 21) years and weighing between 50 and 70 (mean 62) kg participated in the study. Inclusion criteria were: no evidence of cardiovascular, pulmonary, hepatic, renal or gastrointestinal disease, and results from routine laboratory tests, including complete blood count, chemistry tests with liver panel, urinalysis and ECG, within the normal range. Smokers (<15 cigarettes/day) were eligible for the study. No other medication was allowed during the month before the start of the study and during the study (except oral contraceptives). Individuals who had participated in another clinical trial within 90 days prior to the entry to this study were excluded.

Study Design

This was a randomised, single dose, nonblind phase I study with a crossover design. It consisted of two 1-day occasions, each separated by a 1-week washout period. On each occasion a 400mg dose of ibuprofen (administered as a racemic mixture) was given orally with 100ml of water. Ibuprofen was administered as a suspension or as effervescent granules. Both formulations were manufactured at Laboratorios Knoll S.A. BASF Pharma, Madrid, Spain. Participants were admitted to the Department of Clinical Pharmacology, Infanta Cristina University Hospital, on the morning of each occasion. They fasted overnight and took the dose at 08.00. They were served breakfast and lunch at 10.00 and 14.00, respectively. Participants left the hospital 12 hours after drug intake unless otherwise indicated, for example because of the occurrence of adverse events.

Pharmacokinetics

Venous blood samples (5ml) for measurement of racemic ibuprofen were taken from the forearm vein at the following times during the 2 study days: just before drug intake, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours after intake. Plasma was obtained after centrifugation of blood samples and plasma drug concentrations were determined by a validated high resolution liquid chromatography nonstereoselective method published previously.[13] In the ibuprofen plasma concentration range of 0.5 to 50 mg/L the method showed linearity, the mean intra- and interassay coefficients of variation were less than 5%, and the accuracy of the assay was higher than 95%.

Pharmacodynamic Study

Patients

103 febrile children participated in the study. Signed informed written consent was obtained from each patient's parent or legal guardian, and approvals were obtained from the ethics committee of the centres in which the study was carried out. The study was conducted according to the guidelines in the Declaration of Helsinki. Inclusion criteria were children (male or female) with bodyweight ≥25kg and oral temperature before drug intake ≥38°C. Exclusion criteria were severe clinical pathology, neurological and psychiatric disorders, treatment with other antipyretic drugs over the 5 days prior to entry in the study, gastrointestinal, vascular, blood coagulation and visual disorders, or asthma. No concomitant administration of other NSAIDs was allowed for 6 hours before the start of the study. Children who had participated in another clinical trial within 90 days prior to entry into this study were excluded. Table I lists the demographic characteristics of the population enrolled in the pharmacodynamic study.

Table I. Summary of patient characteristics in the efficacy and safety study. Values are means and ranges, except for numbers of patients

Characteristic	Total	Suspension	Granules
Number	103	52	51
Age (y)		8.5 (4-16)	8.7 (5-14)
Bodyweight (kg)		32.5 (25-59)	34.0 (25-70)
Gender			
female	46	24	22
male	57	28	29
Baseline temperature (°C)		39.1 (38.0-40.2)	39.0 (38.0-39.8)
Diagnoses			
tonsillitis	22		
influenza	21		
pharyngitis	17		
respiratory infection	21		
earache	3		
cystitis	2		
abdominal pain	2		
other[a]	21		

a Diagnoses such as brucellosis, headache and sepsis that were reported for only 1 patient in the study.

Study Design

This was a randomised, multicentre, single dose phase III study. Children arrived at the Paediatric Department of the hospitals involved in the study, and after screening they took an oral dose of racemic ibuprofen with a sufficient volume of water. There were no restrictions regarding the time of day for drug intake. Patients were randomly allocated to groups receiving 7 mg/kg of ibuprofen in suspension, or 200 or 400mg of ibuprofen as effervescent granules. Drug formulations were also manufactured at Laboratorios Knoll S.A. BASF Pharma, Madrid, Spain.

Antipyretic Effect

Axillary temperatures were recorded using an electronic clinical thermometer (model OMRON MC-103) at the following times: prior to drug intake and at 0.5, 1, 1.5, 2, 3 and 4 hours after drug administration. Measurements were performed once at each time point.

Data Analysis

During the analysis the population approach was used and the strategy was as follows: the pharmacokinetic model was built first, and using the typical disposition characteristics of ibuprofen given in suspension or in granules, a pharmacodynamic model describing the antipyretic drug effect in each of the children in the pharmacodynamic study was then developed. All analyses were performed with the nonlinear mixed effects modelling program NONMEM, version V.[14]

For each of the analyses, pharmacokinetic or pharmacodynamic, a basic population model was proposed. The basic model is defined as the model adequately describing the mean population and individual tendencies without including any covariates in the model. Based on the basic model, the observations are expressed as follows:

$$OBS_{ij} = f(\theta_i, D, t_j) + \varepsilon_{ij}$$

where OBS_{ij} is the j^{th} observation (plasma ibuprofen concentration or antipyretic effect) in the i^{th} individual, f represents the structural model, θ_i represents the set of the parameters (pharmacokinetics or pharmacodynamics) for the i^{th} individual, D is the administered dose, t_j is the time at which the j^{th} observation was recorded and ε_{ij} represents the residual shift of the observation from the model predictions; ε_{ij} are random variables assumed to be symmetrically distributed around 0 with variance denoted by σ^2. Although in the previous expression an additive model was used to relate observations to predictions, different models (i.e. constant coefficient of variation, slope/intercept) were also explored.

For each of the elements of θ_i, the following model was used:

$$p_i = p_{pop} \cdot \exp(\eta_i)$$

where p_i represents an arbitrary pharmacokinetic or pharmacodynamic parameter of the i^{th} individual, p_{pop} is the mean population parameter estimate and η_i, the shift of the parameter of the i^{th} individual from the population mean estimate, is a random variable assumed to be symmetrically distributed around 0 with variance-covariance matrix Ω with diagonal elements ($\omega^2_1, \ldots, \omega^2_m$), m being the

number of pharmacokinetic or pharmacodynamic parameters estimated in the model.

The expressions used for the pharmacokinetic parameters were based on the following allometric equations:[15]

$$V1_i = (V1 \cdot WT_i/70) \cdot \exp(\eta_{V1})$$

$$V2_i = (V2 \cdot WT_i/70) \cdot \exp(\eta_{V2})$$

$$CLd_i = [CLd \cdot (WT_i/70)^{3/4}] \cdot \exp(\eta_{CLd})$$

$$CL_i = [CL \cdot (WT_i/70)^{3/4}] \cdot \exp(\eta_{CL})$$

where $V1_i$, $V2_i$, CLd_i and CL_i are the initial volume of distribution, volume of distribution of the peripheral compartment, intercompartmental clearance and total plasma clearance in the i^{th} individual, respectively; V1, V2, CLd and CL are the mean population estimate of the initial volume of distribution, volume of distribution of the peripheral compartment, intercompartmental clearance and total plasma clearance, respectively; and η_{V1}, η_{V2}, η_{CLd} and η_{CL} represent the interindividual variability associated with V1, V2, CLd and CL, respectively. WT_i represents the bodyweight of the i^{th} individual.

To select the most important covariates and the functional relationship between the covariate and the parameter, a stepwise generalised additive model based on p_i estimates from the basic population model as dependent variables[16] was performed out of NONMEM with the Xpose program.[17] The covariates tested for significance were T_0 (baseline temperature), age and bodyweight (continuous) and gender and drug formulation (categorical); height was also explored during the pharmacokinetic analysis. The covariate relationships found significant during the previous analysis were tested for significance with NONMEM. To evaluate the significance of covariate effects the following selection criterion was followed: the difference in the minimum value of the objective function (OBJ) provided by NONMEM, between a model with and without a specific covariate relationship was compared with a χ^2 distribution in which a difference of approximately 4, 6 and 11 points was significant at the 5, 1 and 0.1% levels, respectively. The covariance among values of η was also explored at this stage of the analysis.

Because the disposition properties of ibuprofen were studied on more than 1 occasion, the presence of interoccasion variability (IOV) in the disposition parameters was also explored and expressed as follows:[18]

$$p_i = p_{pop} \cdot \exp(\kappa_{1i} \cdot Occ_1 + \kappa_{2i} \cdot Occ_2 + \eta_i)$$

IOV is modelled by $\kappa_{1i} \cdot Occ_1 + \kappa_{2i} \cdot Occ_2$. Occ_1 and Occ_2 have the value 1 for the first and second occasions, respectively, and 0 otherwise, 2 being the number of occasions for each individual. κ_1 and κ_2 are random variables assumed to be symmetrically distributed around 0 with identical variance denoted by π^2.

Pharmacokinetic Models

The disposition of the drug in the body was characterised by compartmental models. Absorption after the administration of the drug in suspension was fast and could be adequately described by a first-order process characterised by a first-order rate constant. However, the absorption profile after the administration of the drug in granules showed a more complex profile. Different absorption models were evaluated. Absorption of ibuprofen from the effervescent granules was described using a model with 2 parallel first-order input sites. In this model a fraction of the administered dose is absorbed with a first-order rate constant, and another fraction of the dose entering into the general circulation is absorbed with a different first-order rate constant.

Pharmacodynamic Models

In order to obtain estimates of the pharmacodynamic properties of ibuprofen administered in suspension and granules in febrile children, the results from the population pharmacokinetic model were used as follows. For each of the patients, a drug concentration versus time profile in plasma was estimated on the basis of: (i) the typical pharmacokinetic parameters obtained for the healthy individuals; (ii) the individual patient's bodyweight; (iii) the allometric models; (iv) the individual dose; and (v) the type of formulation (suspension or gran-

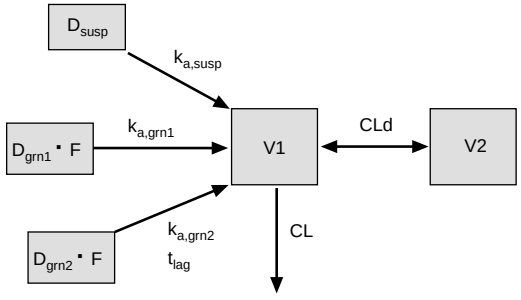

Fig. 1. Schematic representation of the selected pharmacokinetic model. **CL** = plasma clearance; **CLd** = intercompartmental clearance; D_{grn} = administered dose of ibuprofen in effervescent granules; D_{susp} = administered dose of ibuprofen in suspension; **F** = bioavailability of effervescent ibuprofen in the depot compartment; $k_{a,grn1}$ and $k_{a,grn2}$ = first-order rate constants of absorption of effervescent ibuprofen from the depot 1 and 2 compartments, respectively; $k_{a,susp}$ = first-order rate constant of absorption for ibuprofen in suspension; t_{lag} = lag time corresponding to the depot 2 compartment; **V1** = initial volume of distribution; **V2** = volume of distribution of the peripheral compartment.

ules). The individual estimated pharmacokinetic profiles were used together with the individual observed temperature versus time profiles to develop the population pharmacodynamic model.

Mean time of maximum drug concentration in plasma was 0.5 and 1.9 hours after the administration of the drug in suspension or in granules, respectively. Mean time of maximum decrease in body temperature occurred at 3 hours after drug administration. This temporal disequilibrium could be explained (and modelled) under different assumptions, such as that the drug exerts its response by an indirect mechanism of action.[19] In fact, the antipyretic effect of the NSAIDs has been reported to be associated with their ability to inhibit the synthesis of prostaglandin E_2 in the brain.[20] Based on these considerations, the pharmacodynamic model used in the current study is represented by the following expression:

$$\frac{dT}{dt} = k_{syn} \cdot (1 - E_{max} \frac{C^n}{C^n + EC_{50}^n}) - k_{out} \cdot T$$

where dT/dt represents the rate of change in body temperature, k_{syn} is the zero-order rate of formation of the effector (prostaglandin E_2), k_{out} is the first-order rate constant of degradation of the effector, T is body temperature, E_{max} is the maximum attainable drug effect, constrained to be between 0 and 1, EC_{50} is the plasma drug concentration (C) eliciting half the maximum effect, and n is the slope of the k_{syn} versus C relationship. This model assumes that the change in body temperature is related to the change in the rate of synthesis of prostaglandin E_2.

To select the best, median and worst fitted individuals, the mean absolute performance error was computed for each individual. Performance errors were computed as:

$$100 \times (T_{pred} - T_{obs})/T_{obs}$$

where T_{pred} and T_{obs} refer to the model predicted and observed body temperatures, respectively.

Model selection was based on a number of criteria, such as the exploratory analysis of the goodness of fit plots, the estimates and the confidence intervals

Table II. Results from the final population pharmacokinetic model selected

Parameter	Estimate	Interindividual variability[a]
$k_{a,susp}$ (h^{-1})	0.82 (0.45)	31 (0.32)
$k_{a,grn1}$ (h^{-1})	0.61 (0.60)	33 (0.65)
$k_{a,grn2}$ (h^{-1})	2.26 (0.40)	NE
t_{lag} (h)	1.33 (0.09)	16 (0.38)
F_1	0.63 (0.11)	19 (0.24)
V1 (L)[b]	4.4 (0.70)	NE
CL (L/h)[b]	4.05 (0.03)	24 (0.33)
CLd (L/h)[b]	2.09 (0.34)	46 (0.57)
V2 (L)[b]	6.62 (0.14)	65 (0.34)

a Estimates of interindividual variability are expressed as coefficient of variation (%) with relative standard error in parentheses. Relative standard error is standard error divided by the parameter estimate.

b On the basis of the allometric model used during the pharmacokinetic analysis, the units of the disposition parameters (V1, CL, CLd and V2) refer to a standard bodyweight of 70kg.

CL = total plasma clearance; **CLd** = intercompartmental clearance; F_1 = fraction of the dose absorbed from the depot 1 compartment (granules); $k_{a,grn1}$ and $k_{a,grn2}$ = first-order rate constants of absorption for effervescent ibuprofen from the depot 1 and 2 compartments, respectively; $k_{a,susp}$ = first-order rate constant of absorption for ibuprofen in suspension; **NE** = not estimated; t_{lag} = lag time for absorption from the depot 2 compartment; **V1** = initial volume of distribution; **V2** = apparent volume of distribution of the peripheral compartment.

of the fixed and random parameters, and the minimum value of the OBJ value (see earlier in this section).

Results

Pharmacokinetic Study

Figure 1 shows the model used to describe simultaneously the absorption and distribution kinetics of ibuprofen administered in suspension and effervescent granules. For ibuprofen in suspension, the dose reaches the depot compartment from which the drug immediately begins to be absorbed with a first-order rate constant $k_{a,susp}$. For ibuprofen given as effervescent granules, part of the dose (F_1) reaches the depot 1 compartment and part of the dose (F_2) reaches the depot 2 compartment. The sum of F_1 and F_2 was not initially constrained to be less or equal to 1, but results from the modelling process shown that F_2 could be computed as $1 - F_1$. The value of F_1 for ibuprofen given in suspension was assumed to be 1. Drug amounts in the depot 1 and 2 compartments were absorbed with first-order rate constants $k_{a,grn1}$ and $k_{a,grn2}$, respectively. A lag time (t_{lag}) for the absorption process from the depot 2 compartment was also included in the model. This model significantly improved the fit ($p < 0.001$) with respect to simpler models such as zero-order, Michaelis-Menten absorption models, etc. The typical and interindividual variability estimates of the absorption parameters are listed in table II. The typical estimates for $k_{a,susp}$ and $k_{a,grn1}$ were similar, but the use of a common k_a for both formulations made the fit significantly worse ($p < 0.001$). Interindividual variability could only be estimated for $k_{a,susp}$, $k_{a,grn1}$, t_{lag} and F_1. The estimates show a moderate/low variability, since the highest estimate was 33% (for $k_{a,grn1}$).

A 2-compartment model described significantly better ($p < 0.001$) the disposition of ibuprofen compared with 1- or 3-compartment models. No differences in the typical parameter estimates were found based on the characteristics of the formulations. Typical parameters and their estimates of interindividual and interoccasion variability are also shown in table II. Variability could be estimated in CL, CLd and V2, but not in V1. Variability in CL was low (23%) but the estimates for CLd and V2 increased to 46 and 61%, respectively. No covariate effects of age, bodyweight, gender or height were found in any of the pharmacokinetic parameters. Although IOV was also tested in CLd and V2, it was only significant ($p < 0.001$) for CL with an estimate of 20% and a relative standard error of

Table III. Some of the pharmacokinetic models tested in NONMEM during the population pharmacokinetic analysis

Model	Pharmacokinetic model	Objective function
A	Disposition: 1 compartment Absorption (suspension): 1st order; $k_{a,susp}$; $F_1 = 1$ Absorption (granules): 1st order; $k_{a,grn}$; F_1	1280
B	Disposition: 2 compartments Absorption (suspension): 1st order; $k_{a,susp}$; $F_1 = 1$ Absorption (granules): 1st order; $k_{a,grn}$; F_1	1247
C	Disposition: 2 compartments Absorption (suspension): 1st order; $k_{a,susp}$; $F_1 = 1$ Absorption (granules): 2 depot compartments 1st depot: $k_{a,grn1} = k_{a,susp}$; F_1 2nd depot: $k_{a,grn2}$; $F_2 = 1 - F_1$	1128
D	Disposition: 2 compartments Absorption (suspension): 1st order; $k_{a,susp}$; $F_1 = 1$ Absorption (granules): 2 depot compartments 1st depot: $k_{a,grn1} = k_{a,susp}$; F_1 2nd depot: $k_{a,grn2}$; $F_2 = 1 - F_1$, t_{lag}	1108
E[a]	Disposition: 2 compartments Absorption (suspension): 1st order; $k_{a,susp}$; $F_1 = 1$ Absorption (granules): 2 depot compartments 1st depot: $k_{a,grn1}$; F_1 2nd depot: $k_{a,grn2}$; $F_2 = 1 - F_1$, t_{lag}	1096
F	As model E + covariance (η_{CL}, η_{CLd}, η_{V2})	1092
G	As model E + covariance ($\eta_{ka,grn1}$, η_{F1})	1094

a Population pharmacokinetic model selected.

F_1 and **F_2** = fractions of the dose absorbed from the depot 1 and 2 compartments, respectively (the value of F_1 for ibuprofen in suspension was fixed as 1); **$k_{a,susp}$** and **$k_{a,grn}$** = first-order rate constants of absorption for ibuprofen in suspension and effervescent granules, respectively; **$k_{a,grn1}$** and **$k_{a,grn2}$** = first-order rate constants of absorption for effervescent ibuprofen from the depot 1 and 2 compartments, respectively; **t_{lag}** = lag time for absorption from the depot 2 compartment; **η_{CL}**, **η_{CLd}**, **η_{V2}**, **$\eta_{ka,grn1}$** and **η_{F1}** = interindividual variability associated to total plasma clearance, intercompartmental clearance, volume of distribution of peripheral compartment, $k_{a,grn1}$ and F_1, respectively.

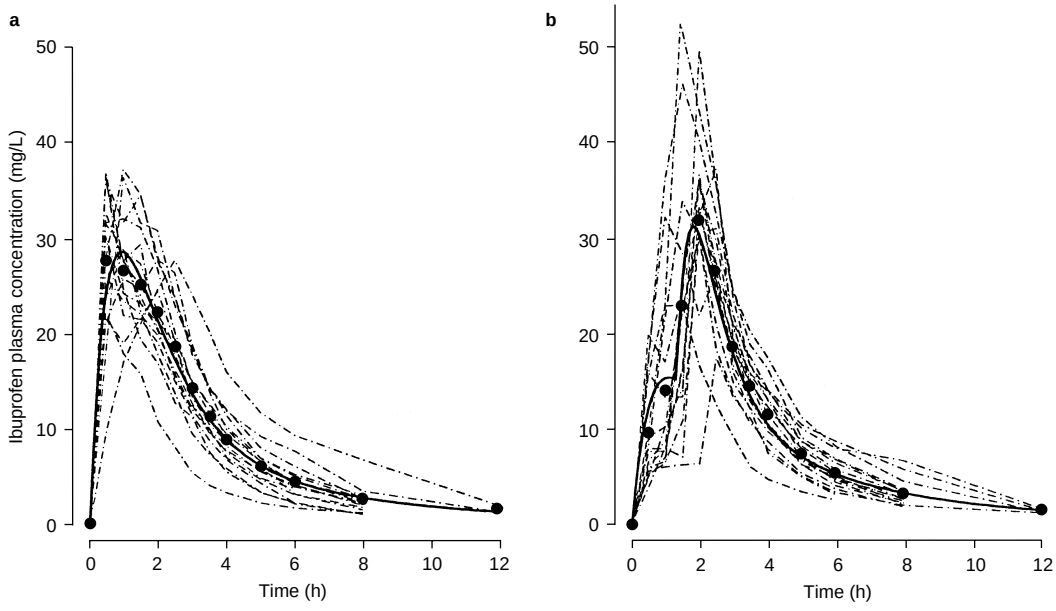

Fig. 2. Individual (broken lines) and mean (points) observed pharmacokinetic profiles of ibuprofen after oral administration of 400mg in suspension (**a**) or as effervescent granules (**b**). Solid lines represent typical model predictions.

0.28. Covariance between values of η was also evaluated, but was found to be nonsignificant ($p > 0.05$). Residual variabilities were modeled by a constant coefficient of variation model and their estimates were 11 and 15% for ibuprofen in suspension and in granules, respectively. Table III lists some of the pharmacokinetic models fitted to the plasma ibuprofen concentration versus time data. Figure 2 shows the mean observed concentration versus time data and the typical model predictions for both formulations.

Pharmacodynamic Study

An inhibitory sigmoidal E_{max} model gave a significantly ($p < 0.001$) better description of the temperature versus time data compared with the linear E_{max} model. The basic population model included interindividual variability terms on the following pharmacodynamic parameters: k_{out}, EC_{50}, E_{max} and T_0, where $k_{syn} = k_{out} \cdot T_0$. The residual variability was modeled with an additive model. The stepwise generalised additive model procedure selected the following as potential covariates: type of formulation (suspension or granules) was selected for EC_{50}, k_{out} and E_{max}; k_{out} was also found to be related linearly with bodyweight, and age was also linearly associated with T_0. When these covariate relationships were tested for significance in NONMEM, no significant ($p > 0.05$) decreases in the minimum value of OBJ were obtained. In addition, the effect of the initial body temperature on E_{max} was also explored. Table IV shows some of the covariate models tested in NONMEM, and table V lists the parameters and interindividual variability estimates of the final selected model (basic population model). The value of k_{syn} computed on the basis of the estimates of k_{out} and T_0 was $45.4 \cdot T_0\ h^{-1}$. Interindividual variability associated with T_0 was estimated as only 0.4%, but on the basis of the OBJ function values its inclusion in the model was justified. Covariance between values of η was found to be nonsignificant. The residual variability was estimated as 1%. Figure 3 shows the mean temperature versus time raw data and the typical model

Table IV. Covariate models tested in NONMEM during the population pharmacodynamic analysis

Covariate model	Objective function	p-Value
Basic model (no covariates)	–284.5	
Suspension: $EC_{50} = \theta_1$ Effervescent granules: $EC_{50} = \theta_2$	–284.5	>0.05
Suspension: $k_{out} = \theta_2$ Effervescent granules: $k_{out} = \theta_3$ Effervescent granules $EC_{50} = \theta_2$	–287.2	>0.05
Suspension: $E_{max} = \theta_3$ Effervescent granules: $E_{max} = \theta_4$	–287.2	>0.05
$k_{out} = \theta_2 \bullet (1 + \theta_3 \bullet WT)$	–284.5	>0.05
$T_0 = \theta_4 \bullet (1 + \theta_5 \bullet Age)$	–285.6	>0.05
$E_{max} = \theta_3 \bullet (1 + \theta_4 \bullet T_0)$	–286.7	>0.05

EC_{50} = plasma drug concentration eliciting half of E_{max}; **E_{max}** = maximum attainable drug effect; **k_{out}** = first-order rate constant of degradation; **T_0** = baseline temperature; **WT** = bodyweight.

predictions for both formulations. Figure 4 shows the individual observed and model predicted profiles for the best, median and worst fitted patients receiving ibuprofen 7 mg/kg in suspension or 200 or 400mg as effervescent granules.

Finally, the implications of the plasma concentration versus time profiles for the time course of drug effect were further explored using computer simulations. Figure 5 shows simulated typical kinetic and effect profiles for both formulations administered as multiple doses of 5 and 10 mg/kg every 6 hours.

Discussion

In this study the pharmacokinetics and pharmacodynamics of 2 oral forms of ibuprofen were studied using the population pharmacokinetic-pharmacodynamic approach. In general, comparison between formulations of ibuprofen was based on measurements obtained from the raw data (i.e. C_{max}, t_{max}, AUC, time to peak effect, duration of effect) and much less effort was made towards quantifying the processes determining the time course of drug effect (absorption, disposition, drug potency or efficacy).

Pharmacokinetics were studied with a well controlled design in a group of healthy young volunteers. Estimates of plasma drug disposition parameters were very similar to those reported previously by several authors and are in accordance with the small volume of distribution and restrictive elimination properties common to most NSAIDs.[21-23] No covariate effect of the type of oral formulation was found in the disposition of ibuprofen in plasma. However, the absorption profile differed markedly between the 2 formulations. Ibuprofen given as effervescent granules showed a complex input profile, as can be observed in figure 2. In order to be able to describe such profiles, a model assuming 2 depot compartments from which the drug was absorbed by first-order kinetics was developed (see fig. 1). This model has a mechanistic interpretation: first, that part of the absorbed dose (63%) which is almost instantaneously removed from the pharmaceutical formulation begins to be absorbed with no delay after drug ingestion with a first-order rate constant ($k_{a,grn1}$) of 0.61 h^{-1}. This estimate was similar to that for ibuprofen in suspension. Secondly, the rest of the dose absorbed (37%) needs a certain time to be removed from the formulation (this time could be represented by t_{lag}) and then it begins to be absorbed with a first-order rate constant ($k_{a,grn2}$) of 2.26 h^{-1}. The fact that $k_{a,grn2}$ is higher than $k_{a,grn1}$ might mean that in that region of the gut ibuprofen absorption is enhanced compared with the previous region. The absorption model built for the effervescent granules has been used previously to describe, for example, the kinetics

Table V. Results from the final population pharmacodynamic model selected

Parameter	Estimate[a]	Interindividual variability
EC_{50} (mg/L)	6.18 (0.14)	62 (0.51)
k_{out} (h^{-1})	1.17 (0.23)	78 (0.45)
E_{max}	0.055 (0.43)	25 (0.26)
T_0 (°C)	38.8 (0.01)	0.8 (0.23)
n	2.71 (0.18)	NE

a Estimates of interindividual variability are expressed as coefficient of variation (%) with relative standard error in parentheses. Relative standard error is standard error divided by the parameter estimate.

EC_{50} = plasma drug concentration eliciting half of E_{max}; **E_{max}** = maximum attainable drug effect; **k_{out}** = first-order rate constant of degradation; **n** = slope of the effect *vs* plasma concentration relationship; **NE** = not estimated; **T_0** = baseline temperature.

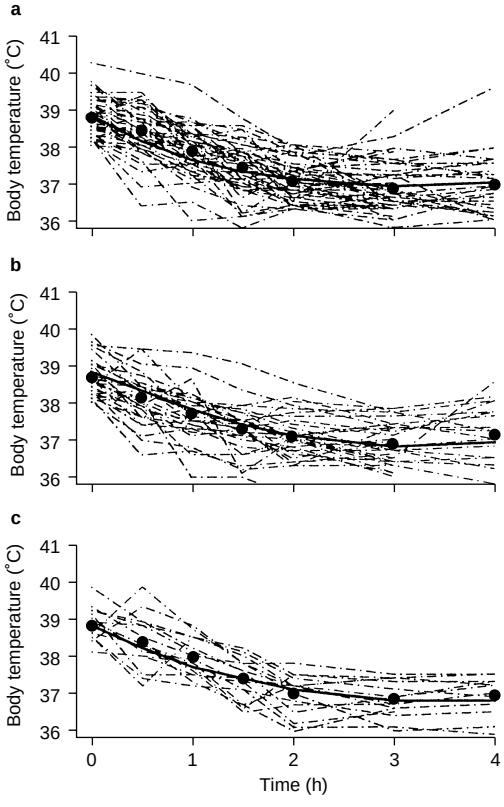

Fig. 3. Individual (broken lines) and mean (points) observed antipyretic versus time profiles of ibuprofen after oral administration of 7 mg/kg in suspension (**a**) or 200mg (**b**) or 400mg (**c**) as effervescent granules to febrile children. Solid lines represent typical model predictions.

of a new controlled-release formulation of oxycodone.[24] The relative bioavailability of the effervescent granules with respect to suspension was 1. The estimates of interindividual variability were moderate (17 to 60%), but these results should be interpreted with caution since the population sample studied was small and very homogeneous. CL was the only pharmacokinetic parameter showing IOV (20%). Since ibuprofen is a restrictively cleared drug, this finding could be attributable to low IOV in protein binding and/or enzymatic activity, which will affect CL proportionally.[23]

The mean t_{max} for ibuprofen in suspension was 0.5 hours. This result is comparable with the value of 0.74 hours reported by Scott et al.[5] after giving ibuprofen in suspension to children with cystic fibrosis. On the other hand, the mean t_{max} of ibuprofen in effervescent granules obtained in this study, 1.9 hours, differs from the value of 0.6 hours reported previously in another study where effervescent ibuprofen was also administered.[25]

The major limitation of this pharmacokinetic analysis, which might have potential implications in the interpretation of the pharmacodynamic results, is due to the fact that only the time course of racemic ibuprofen has been considered. The possibility exists that, despite similar racemic concentrations, the plasma concentration ratio between the active (*S*)- and inactive (*R*)-enantiomers differs between the 2 formulations tested. Jamali et al.[26] observed differences in the *S*/*R* concentration ratio at t_{max} of the (*S*)-isomer for 4 different oral formulations of racemic ibuprofen. On the other hand, Hummel et al.[25] found that the (*S*)- and (*R*)-enantiomers showed similar kinetics in plasma when racemic ibuprofen was given orally as tablets and an effervescent formulation. It is not possible with the data we have presented in the present paper to conclude whether the time course of both enantiomers is similar between the suspension and the effervescent granules. However, on the basis of the results obtained during the pharmacodynamic analysis (see later in this section) we believe that the time courses of the *S*/*R* concentration ratio in plasma for both formulations are comparable.

On the basis of the mean observed values of t_{max} (1.9 and 0.9 hours for effervescent granules and suspension, respectively) and C_{max} (34.6 and 31.1 mg/L for effervescent granules and suspension, respectively), a delayed but similar maximum therapeutic efficacy would be expected for the drug given as granules compared with the drug in suspension. However, when we explored the mean raw data of the time course of the antipyretic effect obtained from the 103 children involved in the efficacy and safety study, we found that the maximum antipyretic effect was similar and occurred at the same time (3 hours after drug administration) for both

formulations. There are 2 possible explanations for this finding, as follows.

(i) As discussed previously, formulation-related variations in the absorption profiles of the 2 enantiomers of ibuprofen may have occurred, and consequently the typical plasma versus time profile for the racemic drug does not reflect properly the profile for the 'active' drug.

(ii) There is evidence suggesting temporal disequilibrium between drug concentration in plasma and the analgesic[27] and antipyretic[10,11] effect of ibuprofen. As an analogy, the effect compartment model was recently revisited from the perspective of poor compliance.[28] It was shown, by means of computer simulations, that the effect of compliance on drug response was more dramatic in the case of drugs for which pharmacological response was directly related to plasma concentration. However, if the drug exerted its response through an effect compartment (or an indirect mechanism), the impact of higher/lower plasma drug concentrations (e.g. the consequences of poor compliance) on the response was much less. These considerations can also be applied to the situation in the current study: different plasma drug concentration versus time profiles are present, not because of poor compliance but because of the different formulations used, and these different pharmacokinetic profiles elicit similar effect versus time profiles.

To explore these possibilities we analysed the antipyretic effect versus time data using pharmacodynamic modelling. During the efficacy and safety study, no plasma drug concentrations were taken; consequently, to develop a model for drug exposure in children we used the model structure, the typical population absorption parameters and the typical disposition pharmacokinetic parameters obtained from pharmacokinetic analysis of the data from healthy young adult volunteers. Each child has his or her own predicted plasma ibuprofen versus time profile based on: (i) drug formulation; (ii) administered dose; (iii) estimates of the disposition parameters obtained for the healthy volunteers; and (iv) bodyweight. The estimates of the disposition parameters obtained for the healthy volunteers are similar to those previously reported from febrile children aged between 3 and 10 years,[29] which makes our approach reasonable, although there are drawbacks such as the fact that we had no control of food intake before drug administration in the efficacy and safety study. A possibility exists that food could affect the absorption profile of ibuprofen from one or both formulations.

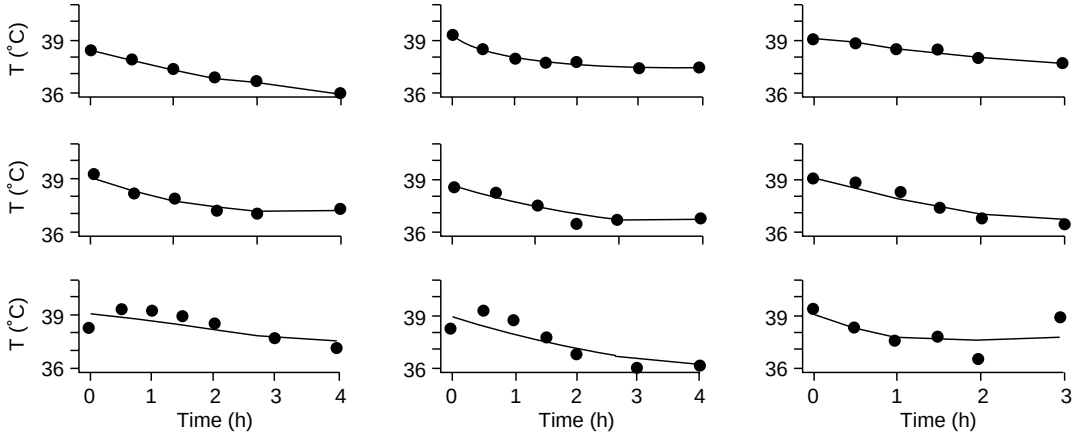

Fig. 4. Individual observed (points) and model-predicted (lines) body temperature (T) versus time profiles for the best (upper panels), median (middle panels) and worst (lower panels) fitted individuals participating in the efficacy and safety study who received ibuprofen 7 mg/kg in solution (first column), 200mg as granules (second column) or 400mg as granules (third column).

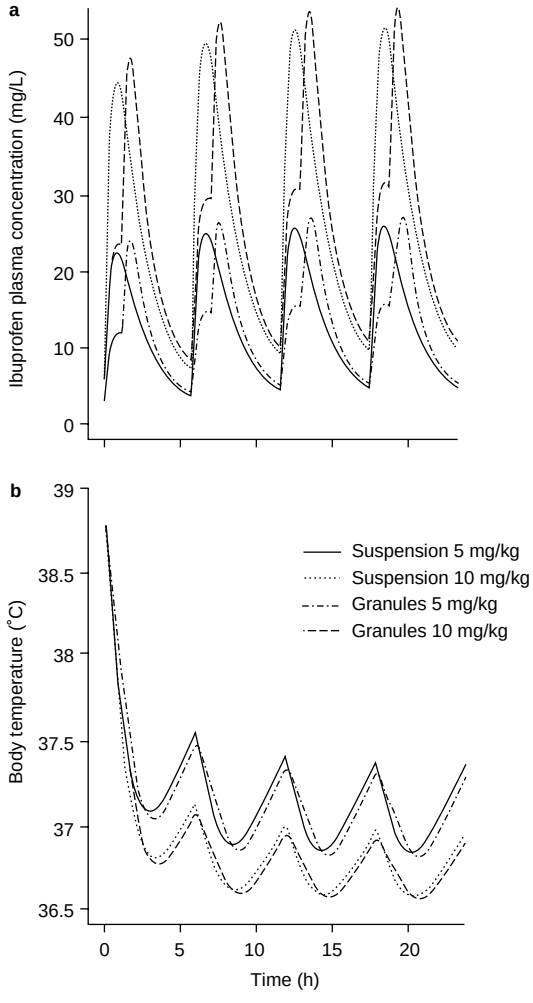

Fig. 5. Simulated typical pharmacokinetic (**a**) and antipyretic effect versus time (**b**) profiles of ibuprofen administered orally at dosages of 5 or 10 mg/kg every 6 hours in suspension or as granules.

The pharmacokinetic-pharmacodynamic model developed showed a very good performance in describing both mean population tendency and individual antipyretic profiles. The pharmacodynamic parameters had reasonable estimates: EC_{50} was estimated to be 6.18 mg/L. This value differs from the 10.1 mg/L estimated reported previously by Garg and Jusko,[11] and differences in the methodology of the analysis could explain this discrepancy; on the other hand the typical values of k_{out} were very similar between the 2 studies (1.17 h^{-1} in the current study *vs* 0.89 h^{-1} in the previous study[11]). In order to interpret the results of the estimates of the pharmacodynamic parameters, it should be taken into account that no placebo group was included in the design; a placebo effect of temperature decreasing with time has been observed by Walson et al.[30] Estimates of the pharmacodynamic parameters could not be compared with those published by Kelley et al.[10] since a linear pharmacodynamic model was used to relate antipyretic effect with estimated drug concentrations in the biophase. Our data support the sigmoidal E_{max} model over the simpler linear model. Since typical pharmacokinetic parameters were used, the interindividual variability associated with pharmacodynamic parameters is likely to be overestimated, since variability of the absorption and disposition processes is also involved; however, estimates of variability were not extremely high: 62, 78 and 25% for EC_{50}, k_{out} and E_{max}, respectively.

The fact that drug formulation was not selected as a significant covariate in any of the pharmacodynamic parameters could be interpreted as an indirect indication that, for these particular oral formulations of ibuprofen, the time course of the active isomer in plasma can be described using racemic concentrations. Age[31,32] and initial temperature[32,33] have been selected in previous studies as significant covariates influencing the pharmacodynamics of ibuprofen regarding its antipyretic properties. We did not find such covariate effects in our data. The fact that in our population the age of the children ranged from 4 to 14 years, whereas Kauffman and Nelson[31] and Wilson et al.[32] studied children aged from 3 months to 10.4 or 12 years, respectively, could explain the discrepancies between the studies. Another issue that should be taken into consideration is that during the analyses performed by Kauffman and Nelson[31] and Brown et al.[33] the effect compartment model, instead of an indirect response model, was used.

We performed computer simulations to extend our results from single doses to multiple doses of

ibuprofen, using a typical regimen of 5 or 10 mg/kg of either formulation every 6 hours (see fig. 5). It can be observed that the differences in plasma drug concentrations between formulations are much less apparent in the time course of drug effect, where the drug begins to exert its action at similar times and to similar extents for both formulations.

Conclusions

After administering ibuprofen in suspension and as effervescent granules to healthy volunteers, drug disposition parameters were not affected by the type of oral formulation. However, absorption was modified: t_{max} values for ibuprofen in suspension and effervescent granules were 0.5 and 1.9 hours, respectively. These differences in absorption could be described by an appropriate pharmacokinetic model. Despite the expected differences in the pharmacokinetic profiles between the 2 formulations, the mean antipyretic effect versus time profiles obtained from 103 febrile children were similar. A pharmacokinetic-pharmacodynamic model was built to describe the time course of the antipyretic effect. No differences in pharmacodynamic parameters were found between formulations. Because of the indirect nature of the effect exerted by ibuprofen, the implications of differences found in the plasma drug concentrations profiles between suspension and effervescent granules are less apparent in the therapeutic response.

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