PHARMACOKINETICS

Population pharmacokinetics of high dose ibuprofen in cystic fibrosis

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Aims: To evaluate ibuprofen population pharmacokinetics in a large series of data collected in children with cystic fibrosis (CF) treated with high doses of ibuprofen (59 patients; 2–18 years), and to identify the main causes responsible for the considerable interindividual variability in ibuprofen serum levels.
Methods: Blood samples were collected during routine clinical care; serum ibuprofen concentrations were determined by HPLC. Fitting of the concentration/time data to a one compartment kinetic population model was performed by a non-linear mixed effect regression method.
Results: Body weight, dose, and ibuprofen dosage form (lysinate salt or the free acid form), for elimination clearance (CL/F); and body weight, dose, and fasting status for the apparent distribution volume (Vd/F) proved to be the covariates with influence in the model. The four factors identified helped to explain part of the interindividual variability observed, but the remaining unexplained variability made therapeutic drug monitoring absolutely essential.

buprofen is a safe and effective orally administered non-steroidal anti-inflammatory drug. High dose ibuprofen administered consistently over four years has been shown to slow deterioration in pulmonary function in children over 5 years of age with mild CF, without unacceptable adverse effects.[1–4]

We studied the population pharmacokinetics of ibuprofen in children with CF with a view to identifying the main factors responsible for the considerable variability observed in ibuprofen serum levels.[1 6–8] Knowledge of these factors should allow prediction of the initial ibuprofen doses required to obtain therapeutically optimum results.

MATERIALS AND METHODS
Patients and sampling schedule
The population pharmacokinetics of ibuprofen were studied in a multicentre survey of 59 children from three hospitals over 1–5 years. All patients were treated with high dose ibuprofen in two different tablets formulations: ibuprofen lysinate (Doctril, Abello Farmacia Lab) and ibuprofen in free acid form (Neobrufen, Knoll Lab). Blood specimens were obtained before and every 30 minutes after ibuprofen administration for three hours. When the free acid form was administered, in some cases sampling was prolonged to four or five hours post-dose, in order to better assess the elimination phase. The initial ibuprofen doses (15–25 mg/kg), calculated according to the recommendations of Konstan and colleagues,[1 6] were later modified to obtain therapeutic peak concentration values (Cmax) of 50–100 mg/l.[1 2] Blood sampling was repeated after changes in the dose or ibuprofen dosage form administered, patient's weight, and clinical supervision. Table 1 shows the demographic and clinical data of the patients.

Analytical technique
Samples of frozen serum from the different hospitals were packed in dry ice and sent to the clinical laboratory, where they were stored at −40°C until analysis. Ibuprofen concentrations were determined by HPLC.[9] Separation was achieved on a pre-packed column (Nova Pak, 5 μm RP 18, Waters) with a variable wavelength UV detector. The detection limit

of the technique was <1 mg/l. The intra- and inter-assay errors had a variation coefficient of <10%.

Population pharmacokinetics analysis
The serum data were fitted to a one compartment open population model with first order absorption and elimination. The corresponding pharmacokinetic parameters, absorption constant (Ka), elimination clearance (Cl/F), and apparent distribution volume (Vd/F)—the latter two normalised by bioavailability (F)—were initially modelled as a function of individual attributes or covariates.

The covariates analysed were continuous (body weight, age, and dose) or categorical (dosage form: ibuprofen lysinate = 0/ibuprofen free acid = 1; and fasting status: fasting = 0/took breakfast half an hour after taking ibuprofen = 1).

The value of the population pharmacokinetics parameters Ka, Cl/F, and Vd/F, the intersubject variability in each parameter (η), and the residual errors (ϵ), that describe the differences between the measured and predicted concentrations were estimated using an extended least squares non-linear regression method and the WINNONMIX computer program (Pharsight Corporation, California). This program also estimates, for each patient, the individual pharmacokinetic parameters of ibuprofen for the kinetic model employed (Cmax), and the time at which the peak is reached (Tmax).

An exponential error model for interindividual variability and an additive error model for residual variability were assumed.

The criteria used in evaluating alternative models included the difference in objective functions (asymptotically χ^2 distributed, p<0.001 being considered to represent a significant improvement in fit), the inspection of weighted residual plots, minimisation of interindividual variances and improvement in their precision, a reduction in the magnitude of the residual variability, and Akaike's information criterion.[10]

RESULTS AND DISCUSSION
Table 2 shows the final model selected (p<0.001) and the ibuprofen population parameter estimates in children with CF.

Table 1 Demographic and clinical data of the patients included in the population study

Variable	
Sex (M/F)	55%/45%
Age (years)	9.18 (4.08) [2–18]*
Body weight (kg)	30.12 (12.43) [12–60]*
Height (cm)	132.20 (21.05) [88–177]*
BMI (kg/m^2)	17.01 (5.17) [4.52–49.51]*
FEV$_1$ (%)	83.49 (15.26) [51–117]*
Ibuprofen dosage (mg/kg)	18.33 (4.43) [4–30]*
IDF (ibuprofen lysinate/ibuprofen free acid)	75%/25%
Fasting status (fasting/took food)	46%/54%

*Mean (SD) [range].
BMI, Body mass index; FEV$_1$, forced expiratory volume in one second; IDF, ibuprofen dosage form.

Table 2 Parameter estimates for the final population model: Ka (h^{-1}) = θ_1, Cl/F (L/h) = (θ_2*W+θ_3*D)*(1−θ_4*IDF), Vd/F (L) = (θ_5*W+θ_6*D)*(1+θ_7*FS)

Parameter	Estimate	SE (%)*	95% CI
θ_1	6.66	31.47	2.52 to 10.80
θ_2	0.07	13.70	0.05 to 0.09
θ_3	0.08	20.84	0.05 to 0.11
θ_4	0.28	22.06	0.16 to 0.41
θ_5	0.10	18.98	0.06 to 0.16
θ_6	0.06	44.41	0.01 to 0.12
θ_7	0.37	45.34	2.52 to 10.80

Interindividual variability: $\omega^2_{Cl/F}$: 75% (CV); $\omega^2_{Vd/F}$: 45% (CV)
Residual variability: σ^2: ±6.74 mg/l (CV=18%)†

W, body weight; D, dose; θ, population specific pharmacokinetic parameter; IDF, ibuprofen dosage form (ibuprofen lysinate=0/ibuprofen free acid=1); FS, fasting status (fasting=0/food=1).
*Standard error of the estimate expressed as coefficient of variation (%).
†For a mean concentration of 38 mg/l.

According to the results obtained, ibuprofen pharmacokinetics depend on the weight, dose, type of formulation, and the fasted or fed state of the patient. The influence of these factors accounts for the difficulty encountered by clinicians in maintaining ibuprofen peak concentrations within the therapeutic range.

Most of the pharmacokinetic parameters of ibuprofen estimated with the final population model were obtained with acceptable precision (table 2). However, the interindividual variability of the parameters was excessively high and it was not possible to estimate that corresponding to Ka. In other population studies on ibuprofen, the interindividual variability of the parameters estimated was also high,[7 8] even in more homogeneous populations.[11] The four factors identified here help to explain part of the interindividual variability observed in the pharmacokinetics of ibuprofen, but the high unexplained variability could be due to the heterogeneous clinical status of the patients and the extent of the pharmacokinetic changes due to CF.[1 12 13] In addition, the extent of absorption is unknown for CF patients; changes in the bioavailability (F) of ibuprofen, not quantified in the model, may have occurred due to varying fasting status and dosage form. All this contributes to increasing the variability in clearance and the apparent distribution volume, which in practice are evaluated as Cl/F and Vd/F, respectively.

The results obtained from the final population model point to the existence of dose dependent kinetics of ibuprofen in the paediatric population studied, affecting the clearance and the apparent distribution volume of the drug. These findings are partially in agreement with those reported by other authors,[14–16] who described the existence of dose dependent kinetics for ibuprofen in adult patients. Likewise, studies in febrile children treated with lower ibuprofen doses (5–10 mg/kg) have not reported modifications in the pharmacokinetic parameters with the dose[17] or modification with low

statistical significance.[18 19] The significant dose dependence observed here could be due to the use of higher doses for efficacy in CF.

The fasting status also significantly affected the population kinetics of the drug.[20] In our study, administration of food after the ibuprofen dosing led to an increase in the Vd/F ratio of ibuprofen. This suggests the possible occurrence of alterations in the bioavailable fraction of the drug (F) and not in the apparent distribution volume (Vd). Thus, for more stable ibuprofen levels daily maintenance of the same dietary behaviour is advised.

As may be explained from the population model, the type of dosage form significantly affects the Cl/F ratio of ibuprofen. The observed reduction in the value of Cl/F when the drug is administered in the free acid form could be related to changes in the bioavailable fraction (F). Figure 1 shows that administration of ibuprofen in the free acid form elicits a slower absorption, leading to a reduction in the maximum serum levels and an increase in the time for the maximum concentration to be reached, as has been shown previously in healthy volunteers.[5] Additionally, the variability in serum levels corresponding to administration of the drug in its free acid form was greater than that observed when it was administered as its lysinate salt. By contrast, our population model does not reflect changes in the first order absorption constant due to the type of formulation used. This can be explained by the reduced use of the formulation corresponding to the free acid form in the population studied. Forty six per cent of the patients were initially treated with ibuprofen free acid, but when the study ended only 25% of the data corresponded to this form. This was because with the lysinate form lower doses were required and lower variability was observed in Cmax levels. In conclusion, emphasis should be placed on the type of formulation to be used at the start of
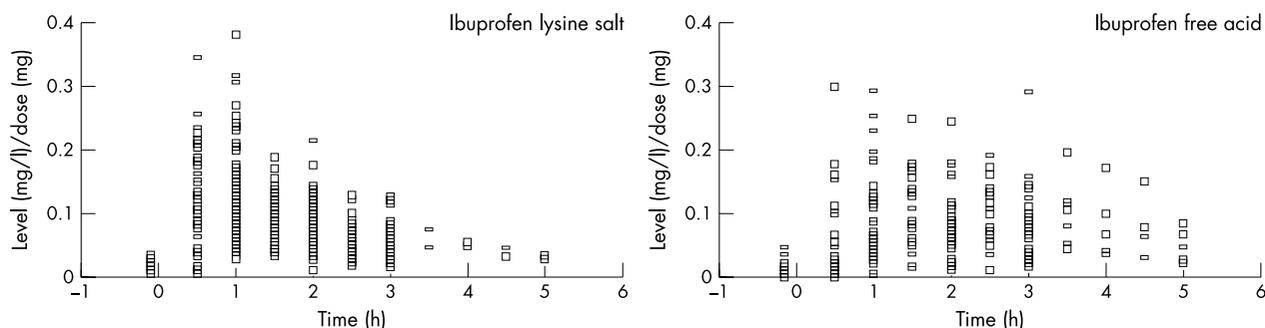

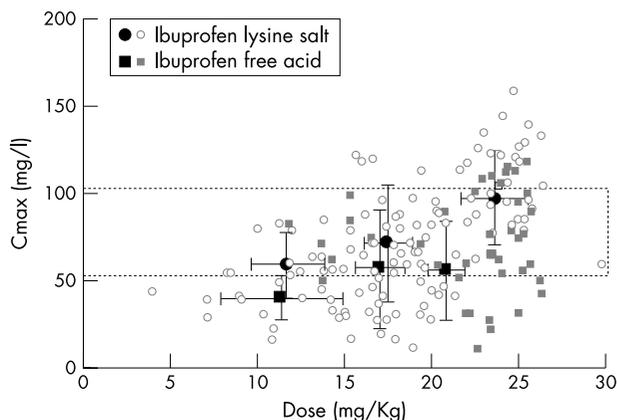**Figure 1** Ibuprofen level/dose ratio versus time for the two dosage forms used in the study.

Figure 2 Relation between predicted peak serum concentrations (Cmax) and dose administered for each of the two formulations used (circles: ibuprofen lysine salt, and squares: ibuprofen free acid form). Grey symbols: individual data; black symbols: the mean value (SD) of Cmax for three dose ranges (<15, 15–20, and >20 mg/kg).

treatment with ibuprofen. In the light of our results, we suggest the use of the lysinate dosage form of ibuprofen instead of the free acid form.

Figure 2 shows the peak concentrations of ibuprofen predicted with our model for the doses administered to each patient. The figure also shows, for each of the two formulations used, the mean value (SD) of Cmax for the three dose ranges administered (<15, 15–20, and >20 mg/kg). The individual data first point to the high interindividual variability in ibuprofen pharmacokinetics. As may be seen, the doses administered did not always afford therapeutic concentrations, and continuous adjustment of the dose through therapeutic drug monitoring was required. These data also reveal the lack of proportionality between the doses administered and the Cmax obtained, reflected in the observed dose dependence. Moreover, the mean values show that identification of any factor that affects the pharmacokinetics of the drug (in this case, the type of formulation administered) helps to differentiate the particular situation of each individual patient. When the lysinate salt is used, doses of 15–20 mg/kg are required for therapeutic levels to be reached in most patients. Doses above 20 mg/kg are associated with a high occurrence of Cmax values above the therapeutic range. In view of the differences in its pharmacokinetics, on administering ibuprofen in free acid form we found lower concentrations. Accordingly, there is a lower likelihood of toxicity when high doses are administered.

In conclusion, in the clinical use of ibuprofen in children with CF, patient weight, the type of formulation, the ingestion or not of food, and the dose may influence ibuprofen levels, resulting in either toxicity or in subtherapeutic effects. Therapeutic drug monitoring of high dose ibuprofen in CF contributes to its optimal use.

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