A comparative population pharmacokinetic analysis for methylprednisolone following multiple dosing of two prodrugs in patients with acute asthma

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Aims To conduct a randomized, parallel group comparison of the population pharmacokinetics of the two methylprednisolone (MP) prodrugs Promedrol (MP suleptanate) and Solo-Medrol (MP succinate) in patients hospitalized with acute asthma.

Methods Ninety volunteers were included in the pharmacokinetic analysis. Each volunteer received a dosage regimen of 40 mg (MP equivalents) i.v. 6 hourly for 48 h. The bio-conversion and disposition of a 40 mg (MP equivalent) i.v. dose of either MP suleptanate or MP succinate to MP was modelled as a first order input, and a mono-exponential elimination phase.

Results Population modelling indicated that the only difference in MP pharmacokinetics between MP suleptanate and MP succinate was in the input rate constant (66.0 h\(^{-1}\) vs 5.5 h\(^{-1}\) respectively). Based on individual Bayesian estimates, the exposure of patients to MP was marginally lower for MP suleptanate although the parameter estimates were not significantly different for half-life (2.7 h vs 3.0 h), steady-state AUC (2007.0 ng ml\(^{-1}\) h vs 2321.0 ng ml\(^{-1}\) h) and steady-state C\(\text{max}\) (698.4 ng ml\(^{-1}\) vs 647.8 ng ml\(^{-1}\)).

Conclusions It was concluded that for the multiple dosage regimen used in patients with acute asthma the systemic exposure to MP following dosing with MP suleptanate is similar to that arising from MP succinate. In addition the differences in the pharmacokinetics for the prodrugs resulted in only a small difference in the relative bioavailability of MP for MP suleptanate (0.94) compared with MP succinate.

Keywords: methylprednisolone, methylprednisolone suleptanate, methylprednisolone succinate, population pharmacokinetics, bioavailability

Introduction

6-α-Methylprednisolone, MP, Medrol\(^{\text{®}}\) has been marketed as an injectable corticosteroid in the form of the sodium succinate ester (MP succinate, Solo-Medrol) for more than 20 years. MP succinate is not stable in solution and is therefore marketed as a freeze-dried product that requires reconstitution resulting in inconvenience, waste, loss of time in preparation, and added cost. Methylprednisolone 21-{8-(2-sulphoethyl) methyl amino}-8-oxo-octanoate, sodium salt (MP suleptanate; Promedrol) is being developed as a pharmaceutical alternative to MP succinate and will be available as a ready to inject solution.

Both MP suleptanate and MP succinate are prodrug esters that are converted to the active agent, MP by the action of esterases in vivo. Studies in animals and man show that the pharmacokinetics of MP released from MP suleptanate are similar to those of MP succinate and that the elimination of MP is the same whether derived from MP succinate or MP suleptanate [1–4]. The rate at which the esterases release MP from MP suleptanate is faster than for MP succinate [3]. For this reason the systemic bioavailability of MP is not identical for the two prodrugs. Conventional bioequivalence studies using a cross-over design have shown that the AUCs for MP are very similar, whereas there are differences in the MP C\(\text{max}\) between the two prodrugs (MP suleptanate higher than MP succinate). However, these differences in C\(\text{max}\) are unlikely to be of clinical significance.

The main purpose of the present study was to examine whether MP suleptanate and MP succinate produce similar safety and efficacy profiles in patients treated with the prodrugs for acute asthma. As part of this study, limited blood sampling of the patients was undertaken in order to investigate the pharmacokinetics of MP in a patient population receiving either MP suleptanate or MP succinate. Essentially this was a population comparative bioavailability study which determined whether a multiple dosage regimen of either prodrug results in similar exposures to MP.

Methods

Study design

This was a multicentre, randomized, double-blind, double-dummy, parallel group comparison of the pharmacokinetics, safety and response to treatment of a fixed dose regimen of the MP prodrugs MP suleptanate or MP succinate in patients hospitalised with acute asthma. Both prodrugs were
supplied by the clinical trials supply department of Pharmacia & Upjohn Inc. (Crawley, UK). The investigational treatment was given for 48 h as a bolus intravenous injection of 40 mg (MP equivalents) at 6 hourly intervals. At 48 h corticosteroid therapy was continued with oral administration of one 32 mg dose of Medrol. Plasma samples were collected from 90 patients (45 patients for each prodrug). A maximum of three plasma samples were collected per patient within the 48th study period. These were drawn after any dose but within three specified time intervals: (i) within 30 min of a dose, (ii) between 30 min and 3 h of a dose, (iii) between 3 and 6 h of a dose.

Patients
Patients included in this study had symptoms consistent with the American Thoracic Society criteria for the diagnosis of asthma. The study was reviewed and approved by the Ethics Committee at each of the five investigative centres. All volunteers received full study details before signing an informed consent form. There were no significant differences between the groups receiving either MP sulleptanate or MP succinate with regard to demographics, cigarette smoking or clinical status. There were slight differences between groups with respect to the mean age of onset of asthma (12.8 years, MP sulleptanate; 16.9 years, MP succinate \( P = 0.093 \)). However, no significant differences were observed for frequency of attacks per month, duration of current attack, previous hospitalisation for asthma, reporting of chronic symptoms (cough, wheeze, spasm and chest pain) or previous requirement for ventilatory support because of asthma. Volunteers were permitted to use a ‘standard’ regimen of concomitant therapies to treat the asthmatic attack. These included inhaled bronchodilators, oral bronchodilators or intravenous theophylline/aminoephyloline.

Drug analysis
Blood samples (5 ml) were collected in EDTA tubes, centrifuged and stored at \(-20^\circ C\) prior to analysis. Plasma samples were analysed for MP concentration at Pharmacia & Upjohn Inc., Crawley, using an in-house developed method combining solid phase extraction with reversed phase h.p.l.c. An aliquot of plasma (0.25 ml or less) was fortified with internal standard solution (dexamethasone), diluted with water and drawn through a primed Bond Elut C2 extraction cartridge. The cartridge was washed with water and methanol:water (20:80 v/v) before elution with acidified acetonitrile:water (50:50 v/v). The eluates were partially evaporated in situ and some or all of the extract analysed by reversed phase h.p.l.c. with u.v. detection at 251 nm.

The h.p.l.c. stationary phase used was Spherosorb ODS II (250 x 4.6 mm) maintained at 45 °C using a forced air column oven. The mobile phase consisted of acetonitrile: trifluoroacetic acid:water (33:0.15:66.85 v/v/v) at 2 ml min \(^{-1}\). Retention times obtained using the described system were: MP, 6.8 minutes and dexamethasone, 7.6 min. The total run time was approximately 10 min. The chromatography was efficient (36,000 theoretical plates m \(^{-1}\)), and robust.

Calibration was carried out using weighted linear regression \((1/x^2)\) and linearity \((r^2)\) was 0.99 or better. Two calibration ranges were used in order to measure the wide range of sample concentrations. The lower limit of quantification for the procedure was 10 ng ml \(^{-1}\) and quality control samples prepared at twice this concentration were measured with a coefficient of variation for the study of less than 20%. At higher concentrations the coefficient of variation was found to be 7.3% or lower.

Pharmacokinetic analysis
Due to the limited plasma concentration data available, pharmacokinetic analysis was carried out using NONMEM (Version IV), which enables estimation of population pharmacokinetic parameters using the method of extended least squares \([5]\).

Pharmacokinetic model Plasma MP levels for either prodrug were best described using a one compartment model with first order input and mono-exponential elimination. Initial estimates of the pharmacokinetic parameters were based on data from an earlier study for a single 40 mg i.v. dose of MP sulleptanate or MP succinate, with model fitting performed in SIPHAR Version 4.0 \([6]\). The first order input of the model described the bio-conversion of MP sulleptanate or MP succinate to MP after an i.v. dose. Steady-state MP levels for both prodrugs administered in a 6 hourly dosing regimen, were reached at 18 h post-dose. The population pharmacokinetic parameters estimated for these data and dosing regimen were clearance \((CL)\), volume of distribution \((V)\), input rate constant \((ka)\). The bioavailability \((F)\) was set to unity for MP succinate, and estimated as a further parameter, relative to MP succinate, for MP sulleptanate.

Pharmacostatistical model Random effects consist of interindividual variability \((\sigma)\) on each parameter and residual variability \((\alpha)\) which encompasses measurement error, model misspecification and interindividual error. A comparison of error models for each parameter showed no benefit in using a more complicated model than a simple additive one to describing the interindividual and residual variation:

\[
CL_j = CL + \sigma_{CL} \\
V_j = V + \sigma_V \\
k_a = k_{a0} + \sigma_{k_a} \\
CP_j = CP + \sigma_j
\]

Covariate analysis The influence of various covariates on the population mean parameter values were investigated. The covariates included indicator variables and the continuous variable body weight. Indicator variables included administered prodrug \((\text{zero}=\text{MP succinate, unity}=\text{MP sulleptanate})\), gender \((\text{zero}=\text{male, unity}=\text{female})\), smoking status \((\text{zero}=\text{non-smoker, unity}=\text{one or more cigarettes smoked a day})\), race \((\text{zero}=\text{white Caucasian, unity}=\text{other race})\). The indicator variables were added individually to the parameters of the basic model. The body weight \((kg)\) of each individual was incorporated into the volume parameter of the model. NONMEM computes a statistic for each analysis, the minimum objective function value, which corresponds to minus twice the log likelihood of the data.
Variables were considered for inclusion in the final model if a significant reduction in the objective function was observed. This statistic can be compared between various model fits using a chi-square ($\chi^2$) test with $q$ degrees of freedom, where $q$ is the difference in the number of thetas estimated between model fits. For a single additional theta added to the model, a reduction in the objective function value of 6.64 units constitutes a significant ($P<0.01$) improvement in the overall fit.

Posterior individual Bayesian analysis: Once the basic NONMEM model had been defined it was possible to calculate individual parameter estimates from the population estimates using Bayesian analysis. This was achieved using the POSTHOC function in NONMEM. In this method the population parameter estimates are used as the Bayesian prior. For the purposes of this estimation, the interindividual error on the input rate parameter ($k_a$) was modelled as exponential (log normal). This was necessary in order to constrain this parameter due to the lack of data available for this phase.

Secondary pharmacokinetic parameters: Individual parameter estimates from Bayesian analysis were imported into SAS/Win Version 6.08 [7] in order to compare the pharmacokinetic parameters for MP suleptanate relative to MP succinate. The mean (± s.e. mean) $t_{1/2,z}$ for patients was estimated as $0.693/\tau$, where $\tau$ was obtained from the individual estimates of CL and $V$ ($\tau=CL/V$). The area under the concentration time curve (AUC) at steady-state was estimated from individual parameter estimates of CL corrected for bioavailability ($F$) using the following equation:

$$AUC_{SS} = \frac{F \cdot DOSE \cdot CL}{CL}$$

Steady-state $t_{max}$ ($t_{maxss}$) and $C_{max}$ ($C_{maxss}$) were calculated using the following equations:

$$t_{max} = \frac{\ln \left( \frac{1}{2} \right)}{k_a - \lambda_a}$$

$$C_{maxss} = \frac{F \cdot DOSE \cdot k_a}{V \cdot (k_a - \lambda_a)}$$

where $\tau$ is the dosing interval of 6 h.

Results

Plasma samples for pharmacokinetic analysis over a 48 h period were available from 90 patients participating in the study. A reasonable fit was obtained for the MP plasma concentration time data for both MP suleptanate and MP succinate using a first order input with mono-exponential elimination despite the high interindividual variability in plasma concentrations for both formulations. Improvements to the basic model fit were made by the addition of covariates individually to the parameters (Table 1). Figure 1 shows NONMEM predicted population values for the final model fit superimposed over the observed data points as a curve. Pharmacokinetic parameter estimates for the final model fit are shown in Table 2. The mean (± s.e. mean) individual Bayesian estimates of MP clearance for MP suleptanate relative to MP succinate were similar (MP curve). Pharmacokinetic parameter estimates for the final model fit are shown in Table 2. The mean (± s.e. mean)
were also comparable for the two prodrugs (MP suleptanate 2.7 h; MP succinate 3.0 h) as was steady-state AUC (MP suleptanate 2007.0 ng ml\(^{-1}\) h, MP succinate 2321.0 ng ml\(^{-1}\) h). Although the estimated \(C_{\text{max}}\) values were higher for MP suleptanate (698.4 ng ml\(^{-1}\)) than MP succinate (647.8 ng ml\(^{-1}\)), this difference was not significantly different due to the higher variability observed for the MP suleptanate estimate.

The only indicator variable that explained some of the variability in the model fit was the administered prodrug. The input rate constant (\(k_i\)) for MP was higher for MP suleptanate than MP succinate, as indicated by a significant (\(P<0.001\)) decrease in the minimum objective function value.

### Discussion

The formation of MP from a 40 mg (MP equivalent) i.v. dose of either MP suleptanate or MP succinate could be modelled as a first order input phase. A basic population fit to the data was achieved using this phase followed by mono-exponential elimination. Additive errors (exponential on the input rate for POSTHOC analysis) specified on both the pharmacokinetic and residual error terms of this model adequately described the variability both within and between subjects in the study. From this basic model it was evident that differences between many of the pharmacokinetic parameters for MP suleptanate and MP succinate were small. In this analysis the AUC for MP suleptanate (2321.0 ng ml\(^{-1}\) h) was slightly higher than that for MP suleptanate (2007.0 ng ml\(^{-1}\) h). Estimated \(C_{\text{max}}\) values based on final NONMEM parameter estimates were not significantly different for MP suleptanate (698.4 ng ml\(^{-1}\)) and MP succinate (647.8 ng ml\(^{-1}\)). Half-lives were similar for MP plasma concentrations of the two prodrugs (MP suleptanate, 2.7 h; MP succinate, 3.0 h). The AUC for MP succinate was of a similar order to MP suleptanate despite the faster rate of formation of MP from MP suleptanate (\(t_{\text{max}}\) 0.07 h vs 0.6 h). The bioavailability of MP suleptanate relative to MP succinate was approximately 94%.

These observations indicate that in asthmatic patients any minor differences in the population pharmacokinetic parameters for MP suleptanate compared to MP succinate are unlikely to be significant in terms of safety and efficacy.

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### References

4. NONMEM Users Guide, NONMEM project group, University of California, San Francisco.

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