DETERMINATION OF THE PHARMACOKINETIC
PARAMETERS OF MELOXICAM IN HEALTHY PAKISTANI
VOLUNTEERS USING NON-COMPARTMENTAL ANALYSIS

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ABSTRACT:
The aim of the present work was to determine pharmacokinetic parameters of meloxicam in local population of Pakistan first time using non-compartmental analysis and to detect any difference which might not be apparent by compartmental analysis which we reported earlier in our population. The study was conducted in 12 healthy male volunteers who receive 30 mg (4x7.5 mg tablets), reference and test tablets according to a randomized 2-way cross-over design. Blood samples were collected at appropriate time intervals up to 96 hrs post dose and drug concentrations was monitored by a validated HPLC method. Statistical tests of the pharmacokinetic parameters was performed by ANOVA that include sequence, subjects within sequence, period and treatment effects ($\alpha = 0.05$). Various pharmacokinetic parameters were determined using non-compartmental method of analysis and a non significant difference were detected by ANOVA analysis but interethnic differences were found in the pharmacokinetics of meloxicam. Thus by using non-compartmental approach, further insight regarding the in vivo performance of meloxicam in local population were highlighted that give an opportunity to detect any difference in pharmacokinetics that might not be apparent by the compartmental analysis of the data. It seems that further studies are mandatory to confirm our findings.

Keywords: Pharmacokinetic parameters, meloxicam, ANOVA, non-compartment

INTRODUCTION

The compartment model concept is essential for understanding the principles of pharmacokinetics. However, in recent years the compartment model independent analysis has gained increasing attention and application (Ritschel, 1992). More investigators and clinicians who use pharmacokinetics are turning to non-compartmental approaches that can be applied to all drugs (Gibaldi, 1991). The reason may be that the human body is in reality a multimillion compartmental model, but the most sophisticated kinetic multi-compartment model may have only very few compartments (Ritschel, 1992). Another reason is that for clinical application of pharmacokinetics it is neither possible to obtain a large number of blood samples to properly characterize a multi-compartmental concentration-time course, nor is it necessary because dosage regimen and dosage regimen adjustment require only a few parameters (Ritschel, 1992).

Meloxicam (CAS 71125-38-7) is comparatively a new non-steroidal anti-inflammatory drug which was developed for the treatment of osteoarthritis and rheumatoid arthritis. The pharmacokinetic profile of meloxicam is characterized by almost complete absorption over a prolonged phase, avoiding high initial drug concentration, bound to plasma proteins by more than 99.5% and has an elimination half-life of 20 hr (Türck et al., 1997). Meloxicam pharmacokinetic data
has been reported for Germans (Türck et al., 1997), Chinese (Xu et al., 2001), Indians (Rani et al., 2004) and Mexicans (Carrasco-Portugal Mdel et al., 2005). However, pharmacokinetic data of meloxicam in Pakistani population is not available in the literature. The aim of the present work was to determine pharmacokinetic parameters of meloxicam in local population of Pakistan first time using non-compartmental analysis and to detect any difference which might not be apparent by compartmental analysis which we reported earlier in our population (Hasan et al., 2008b).

MATERIAL AND METHODS

Material and methods described elsewhere (Hasan et al., 2008a). Briefly, the study was conducted in 12 healthy male volunteers who received 30 mg (4x7.5 mg tablets), reference formulation (Mobic® 7.5 mg tablets; manufacturer : Boehringer Ingelheim Pharma GmbH & Co. KG for Boehringer Ingelheim International GmbH Ingelheim am Rhein Germany) and test formulation (Xobix® 7.5 mg tablets; manufacturer : Hilton Pharma (Pvt.) Ltd., Karachi, Pakistan) according to a randomized 2-way cross-over design. The study was approved by Board of Advance Studies and Research (BASR), university of Karachi and conducted according to standard guidelines. The volunteers were recruited after medical examination by a registered physician and routine laboratory tests results. Detailed information was given by the principal investigator to all the participants regarding the study, its objectives, importance and protocol. All participants provided written informed consent before inclusion in the study. Blood samples were collected at appropriate time intervals according to the protocol up to 96 hrs post dose and drug concentrations was monitored by an HPLC method reported by Dasandi et al., 2002 with modification using external standard method. This method was validated for the present study and both intraday and interday accuracy and precision were well within acceptable range with limit of quantification of the method was 0.1 µg/ml. Plasma was harvested immediately after collection of blood samples by centrifugation, coded and stored at –20°C until analyzed. Pharmacokinetic parameters were determined by Kinetica™ software (version 4.4.1, Thermoelectron corporation, Philadelphia, USA). Statistical tests of the pharmacokinetic parameters was performed by ANOVA that include sequence, subjects within sequence, period and treatment effects (α =0.05).

RESULTS AND DISCUSSION

Both brands of meloxicam were well tolerated by all the volunteers in both phases of the study. Drug related side-effects were not observed in any of the volunteer. There were no drop-outs necessitating volunteer withdrawal from the study and all participants were discharged in good health condition. The meloxicam was measurable at the first sampling time (1 hr) in all the volunteers and measurable titer was found in case of each brand even after 96 hours of administration.

A comparison between the mean±SD values of the pharmacokinetic parameters obtained from plasma concentration time curve for both formulations are presented in Table 1. AUC (area under the plasma level time curve), AUMC (area under the first moment curve), MRT (mean residence time), Cl (clearance) and Vz (apparent volume of distribution) for Mobic® were, 90.40±15.57 µg.hr/ml, 11298±3862 µg.h²/ml, 118.7±20.84 hr, 0.34±0.06 L/hr, 42.73±3.47 L and for Xobix® were, 82.29±10.65µg.hr/ml, 10022 ± 2943 µg.h²/ml, 116.6±21.72 hr, 0.37±0.05 L/hr, 45.79±5.44 L respectively. A non-significant difference at 0.05 level of significance was detected in case of all parameters except in case of AUC where a significant difference was observed in treatments but a non-significant difference was detected in case of sequence, subjects within sequence and periods respectively. The observed differences in extent of absorption may be due to variations in the GI tract of the volunteers, formulation differences etc. (Hasan et al., 2008a). The mean residence time of the drug estimated in present studies indicates that the
drug persists for longer time in body by reference formulation as compared to test formulation. Two previous studies had cited values of MRT which is 37.6 hr (Busch et al., 1991) and 34.2 hr (Türck et al., 1997) obtained after oral administration of 30 mg meloxicam in a German population. Our results are almost 3 times high as compared to Busch et al., 1991 and approximately 3.4 times higher as compared to Türck et al., 1997. Thus drug accumulation in the body for long term use of the drug is expected in local population. In case of clearance, when the results were compared with the reported values, a lower clearance of drug was found in Pakistani population. In this regard 0.528 L/hr (Busch et al., 1991) and 0.489 L/hr (Türck et al., 1997) was reported in German population following oral administration of 30 mg meloxicam and 0.44 L/hr (Rani et al., 2004) in an Indian population following oral administration of 15 mg meloxicam. Carrasco-Portugal Mdel el al., 2005 in a study conducted in a Mexican population had reported a CI value of 0.288 L/hr following oral administration of 7.5 mg meloxicam which was lower as compared to Germans and Indian subjects, but was in agreement with the Chinese subjects. These results advocate that there are interethnic differences in the pharmacokinetics of meloxicam (Carrasco-Portugal Mdel et al., 2005) that might be due to the involvement of CYP2C9 (Xu et al., 2001). In case of apparent volume of distribution (Vz), Türck et al., 1997 had reported Vz as 14 L after oral administration of 30 mg meloxicam in healthy volunteers. Similarly in another study conducted by Rani et al., 2004 in Indians, 19 L was reported which is significantly greater than that reported in other study after administration of 15 mg meloxicam (14.7 L; Türck et al., 1997). We in the present work also have found high Vz (43 L and 46 L; reference and test formulations respectively) in Pakistani population. It seems that in the local population of Pakistan as well as of India, a relatively major portion of administered dose is distributed into extracellular space and tissues and caution is therefore required in the selection of dose to overcome any side effects due to accumulation of drug in the body on long term use of the drug.

**CONCLUSIONS**

Various pharmacokinetic parameters of meloxicam were determined in a Pakistani population first time using non-compartmental method of analysis and a non-significant difference were detected by ANOVA which is in line with the compartmental analysis reported earlier in the local population. This indicates in statistical terms that both formulations under study belong to same population. Our results also advocates that interethnic differences exist in the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Reference formulation</th>
<th>Test formulation</th>
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<tbody>
<tr>
<td>AUC</td>
<td>µg.hr/ml</td>
<td>90.40±15.57</td>
<td>82.29±10.65</td>
</tr>
<tr>
<td>AUMC</td>
<td>µg.hr²/ml</td>
<td>11298±3862</td>
<td>10022±2943</td>
</tr>
<tr>
<td>MRT</td>
<td>hr</td>
<td>118.7±20.84</td>
<td>116.6±21.72</td>
</tr>
<tr>
<td>Cl</td>
<td>L/hr</td>
<td>0.34±0.06</td>
<td>0.37±0.05</td>
</tr>
<tr>
<td>Vz</td>
<td>L</td>
<td>42.73±3.47</td>
<td>45.79±5.44</td>
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AUC = area under the plasma level time curve, AUMC = area under the first moment curve, MRT = mean residence time, Cl = clearance, Vz = apparent volume of distribution.
pharmacokinetics of meloxicam. Thus by using non-compartmental approach further insight about the in vivo performance of meloxicam in local population were highlighted that give an opportunity to detect any difference in pharmacokinetics that might not be apparent by the compartmental analysis of the data. It seems that further studies are mandatory to confirm our findings.

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REFERENCES


