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Disposition of metformin on concomitant administration of erlotinib and meloxicam in SCID mice

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Abstract
Pharmacokinetics of metformin was evaluated following its single dose administration alone and administered with erlotinib and/or meloxicam in SCID mice. Following administration of metformin as a single drug in male SCID mice, the mean values of observed peak plasma drug concentration (C_{max}), time of maximum concentration (T_{max}), area under plasma drug concentration-time curve ($AUC_{0-\infty}$), volume of distribution (Vz), elimination half-life ($t_{½\beta}$) and total body clearance (Cl) were 6277.75 ± 404.25 ng/ml, 0.61 ± 0.10 h, 17218.83 ± 885.71 ng.h/ml, 28950.33 ± 3629.19 ml, 3.36 ± 0.27 h and 5897.32 ± 350.95 ml/h, respectively. Erlotinib and/or meloxicam administration was found to alter pharmacokinetic profile of metformin in SCID mice. Thus, close therapeutic monitoring should be followed for long term concomitant administration of these drugs. However, study on clinical pharmacokinetic interaction of these drugs is required to evaluate interaction in human patients.

Keywords: Pharmacokinetic, metformin, erlotinib, meloxicam, SCID mice

1. Introduction
The metabolic disorder like diabetes having multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism [1]. Currently diabetes mellitus is a great threat for human being as well as dogs. The prevalence and incidence of diabetes is increasing in most populations, being more prominent in many developed and developing countries. It has been documented that people with diabetes are at significantly higher risk for many forms of cancer. Type 2 diabetes and cancer share many risk factors [2].

Antidiabetic drug like metformin inhibiting mTOR through AMP activated protein kinase (AMPK) pathway which may be a promising agent for cancer patient with diabetes as it has been found to increase survival rate of cancer patients [3-4]. Diabetic patients with lung cancer who are previously exposed to metformin are less likely to present with metastatic disease and may survive longer [5-7].

Overexpression of epidermal growth factor receptor (EGFR) and HER-1/ErbB1 are associated with several malignancies in human and animals [8]. EGFR tyrosine kinase (TK) can be considered as an important target for therapeutic intervention in various tumors [9]. Erlotinib is a potent selective inhibitor of the EGFR tyrosine kinase to treat patients with non–small cell lung cancer (NSCLC) [10]. Similarly, during the last decade, many studies have shown that Non-steroidal anti-inflammatory drugs (NSAIDs) may have potential as a chemopreventive agent for cancer [11-14]. Expression of COX-2 is up-regulated in both human cancers and chemically induced cancers in laboratory animals [15-17]. COX-2 inhibitors exibits an important role as chemopreventive in cancers including non-small cell lung cancer (NSCLC) [15, 18-20]. Meloxicam is NSAID of the oxicam class having anti-inflammatory, anti-exudative, analgesic and antipyretic effects by inhibition of prostaglandin synthesis and cyclooxygenase [21-23]. In addition to this malignancy being treated by some specific proven drugs, several malignancy in human and animals are also observed with other disease condition. Therefore, a combination of metformin, erlotonib and meloxicam may be promising chemopreventive strategy in diabetes patients with cancer. However, combination therapy may produce pharmacokinetic interaction and leads to unwanted therapeutic outcome. Metformin pharmacokinetics in mouse tumors was evaluated by Dowling *et al.* [24]. However, pharmacokinetic interaction of metformin with erlotinib and meloxicam has not been studied. Considering the SCID mice one of the worthy laboratory animal models for research in

oncology, present study was planned to study the impact of administration of erlotinib and/or meloxicam on pharmacokinetics of metformin in male SCID mice.

2. Materials and Methods

2.1 Experimental animals and conditions

Total of ninty six severe combined immunodeficient (SCID) male mice of 5-8 weeks of age were used to conduct the study which were obtained from in-house breeding stock as well as maintained at Animal Research Facility, Zydus Research Centre, Cadila Healthcare Ltd., Ahmedabad, India. Sterilized conventional polypropylene cages in animal isolators were used to house all mice in groups of 3 mice. Sterilized corncob was used as bedding material (changed twice a week) which was analyzed for pesticide and microbial contaminants. The temperature and humidity in the experimental room were 22 ± 3 ºC and 30-70%, respectively. The light:dark cycle of 12:12 hours throughout the study period was followed. Gamma irradiated laboratory animal diet (Teklad 18, Rodent Pellet feed, Harlan laboratories, USA) and purified autoclaved drinking water (ad libitum) were provided to experimental animals. All necessary standard husbandry procedures were followed to provide stress free environment to animals and seven days acclimatization period was observed before experiment. Veterinary examination was performed before randomization and animals found healthy. The experimental protocol for general procedures and use of animals for conducting this study was approved by the Institutional Animal Ethics Committee (IAEC).

2.2 Randomization and grouping of animals

All animals were randomly assigned to four treatment groups as shown in Table 1. Each group consisting of total 24 mice, which were further randomly divided into 4 sub-groups (A, B, C and D) of 6 animals each. Total twelve blood sampling time points were distributed among the 4 sub-groups of 6 animals each (each animal/sub group was not bled more than three time points). The same procedure of blood collection was repeated for other sub group of each treatment groups. The single time point concentration data set was made by clubbing and sequential arranging of all samples as per time points from different sub group.

2.3 Drugs and chemicals

Metformin, erlotinib, meloxicam and bisoprolol pure powder were obtained from Ms. Zydus Research Centre, Ahmedabad. Acetonitrile of HPLC grade was purchased from Merck India Ltd., Mumbai. Methanol was procured from SD Fine Chemical Ltd., Mumbai. Twin-80 (polysorbate) was procured from Merck, Germany and hydroxylpropyl methylcellulose (HPMC) was procured from Colorcon Asia Pvt. Ltd.

2.4 Administration of drugs and sampling

Metformin, erlotinib and meloxicam were formulated in Tween 80 and in 2% hydroxypropyl methylcellulose (HPMC). The concentration strength of drug was adjusted with 2% HPMC by keeping Tween 80 concentration at 0.25% in final formulation. Doses were calculated according to body weight of animals and administrated as per concentration strength of formulation. Metformin (100 mg/kg) and erlotinib (30 mg/kg) were administered by oral route using oral gavage needle whereas meloxicam (20 mg/kg) was administered by intraperitoneal route with sterile 1ml tuberculin syringe and needle of 26G (0.45mm x 13mm).

Blood samples (0.25 ml) were collected from retro-orbital plexus under light anesthesia in 0.5 ml capacity centrifuge tube at 5, 10, 20, 40 minutes, 1, 2, 4, 6, 8, 12, 24 and 48 hours after administration of drug and/or combination of drugs. From each sub group, blood samples at 3 time points were collected. Blood samples were collected from all animals in heparinized tubes and centrifuged at 5000 rpm for 10 minutes at ambient temperature to obtain plasma. Separated plasma was transferred to labelled cryovials and stored at - 70 °C until analysis of drug which was carried out usually within a week.

2.5 Metformin Assay

The plasma samples (150 µL) were transferred in 2 ml micro-centrifuge tube to which 5 µL of working solution (10µg/ml) of bisoprolol as an internal standard was added. The contents were mixed by vortexing for 30 seconds. Each sample was added with 800 µL of acetonitrile for plasma protein precipitation and vortexed for 1 minute. Samples were centrifuged at 10,000 rpm for 5 minutes. The supernatant was transferred in HPLC vials and 5 µL was injected using auto sampler (SIL-HTc Auto sampler, Shimadzu, Japan) in LC system (Shimadzu Corporation, Koyoto, Japan) with MS-Ms (API 3200 LC-MS/Ms system, PE SCIEX, Canada). The temperature of auto sampler was 10°C. YMC CN (150 mm x 4.6 mm), 5µm column was used for the separation of metformin at ambient temperature. Metformin eluted at 2.35 ± 0.5 minutes and bisoprolol at 2.75 ± 0.5 minutes with a total run time of 6.2 minutes. Ions were generated using electrospray ionization and detected in the positive-ion mode. The mobile phase consisted 5mM Ammonium Formate + 0.13% Formic acid in water (Solution A) and Acetonitrile (Solution B). Both solutions were used to make the mobile phase using gradient system with different ratio of solution A and B at time 0.01 (45:55), 3 (20:80), 4 (20:80) and 4.5 (45:55) minutes. The mobile phase was pumped at the flow rate of 1.0 ml/min (LC-20-AD, Prominance, Pump, Shimadzu, Japan). Ion spray voltage and temperature in detector were 4500 V and 550 ˚C, respectively. Dwell time was 300 Seconds.

The methodology was validated by spiking the mice plasma samples with known amounts of metformin. Accurately weighed 10.0 mg of metformin pure API grade powder was dissolved in diluent (methanol: water in the ratio of 80:20) to make the concentration of 1,000 µg/ml (Stock solution A). Similarly, 1.0 mg of bisoprolol was dissolved in the diluents to make the concentration of 10 µg/ml (Stock solution B). Working solutions for calibration standards and quality control (QC) samples of metformin were prepared from the stock solution A in the range of 1000 to 80,000 ng/ml. Working solution of internal standard was prepared by diluting 0.5 ml of stock solution B up to 10.0 ml with diluent in volumetric flask to get final concentration of 0.5 µg/ml. Calibration samples consisted of eight different concentrations of metformin over the range of 1000 to 80,000 ng/ml in the diluents and plasma. The low, medium and high quality control samples (1500, 8000, 80,000 ng/ml) were prepared independently in diluent and plasma. All QC samples in the plasma were treated similar to the method described above. The mean recovery of erlotinib from the plasma was ≥ 95% at 100 ng/ml (LLOQ). The linearity was observed from 1000 to 80,000 ng/ml with mean correlation coefficient (R^2) of 0.9995. Intra-day and inter-day precision (±15%) and accuracy (±10%) were within standard limits.

Validation parameters indicated that the method was reliable, reproducible and accurate.

2.6 Pharmacokinetic and statistical analysis

Various pharmacokinetic parameters were determined using WinNonlin software (Version 5.2.1, Pharsight Corporation, USA) by non-compartmental analysis. The data obtained for pharmacokinetic parameters were presented as Mean ± SEM and analyzed statistically using unpaired two tail `t` test. Where $p \leq 0.05$ was considered as statistically significant and $p \leq 0.01$ was considered as statistically highly significant.

3. Results

In the present study, the metformin in plasma was detected in samples collected up to 12 h in animals of all groups. Semi-logarithmic plot of plasma metformin concentration following single dose administration alone, in combination with erlotinib and/or meloxicam are graphically presented in Figure 1. Pharmacokinetic parameters calculated from plasma concentration–time profile after single dose administration of metformin alone and in combination with erlotinib and/or meloxicam in male SCID mice are depicted in Table 2. Following administration of metformin as a single drug in male SCID mice, the mean values of observed peak plasma drug concentration (C_{max}), time of maximum concentration (T_{max}), area under plasma drug concentration-time curve ($AUC_{0-\infty}$), volume of distribution (Vz), elimination half-life ($t_{½\beta}$) and total body clearance (Cl) were 6277.75 ± 404.25 ng/ml, 0.61 ± 0.10 h, 17218.83 ± 885.71 ng.h/ml, 28950.33 ± 3629.19 ml, 3.36 ± 0.27 h and 5897.32 ± 350.95 ml/h, respectively.

Table 1: Experimental outline showing animal number and data set number for various treatment groups.

Group No.	Treatment Group	Cage No.	Animal No.	Data Set No.
I	Metformin	1-8	1-24	1-6
II	Metformin + Erlotinin	9-16	25-48	7-12
III	Metformin + Meloxicam	17-24	49-72	13-18
IV	Metformin + Erlotinin + Meloxicam	25-32	73-96	19-24

Final data set was prepared for six animals by pooling data of sub groups.

Table 2: Pharmacokinetic parameters of metformin following single dose administration (100 mg/kg, p.o) alone in combination with erlotinib (30 mg/kg, p.o) and/or meloxicam (20 mg/kg, i.p) in male SCID mice

PK parameters	MET	MET + ERT	MET + MEX	MET + ERT + MEX
T_{max} (h)	0.61 ± 0.10	0.39 ± 0.09	0.56 ± 0.07	0.33 ± 0.00
C_{max} (ng/ml)	6277.75 ± 404.25	7250.65 ± 487.30	8663.34 ± 464.89	9490.58 ± 963.64**
$t_{1/2\beta}$ (h)	3.36 ± 0.27	2.33 ± 0.30	1.79 ± 0.21**	2.58 ± 0.31
$AUC_{(0-\infty)}$ (ng.h/ml)	17218.83 ± 885.71	17672.48 ± 454.97	23339.74 ± 1314.84**	24658.04 ± 1303.61**
Vz (ml)	28950.33 ± 3629.19	18957.40 ± 2289.64*	11329.62 ± 1581.91**	15338.18 ± 2005.80**
Cl (ml/h)	5897.32 ± 350.95	5678.84 ± 158.06	4356.26 ± 255.94 **	4124.21 ± 261.29**
MRT (h)	2.64 ± 0.12	2.35 ± 0.14	2.20 ± 0.06	2.59 ± 0.11

*Significant at $p<0.05$, **Significant at $p<0.01$; MET: Metformin; ERT: Erlotinib; MEX: Meloxicam; T_{max}: Time of maximum drug concentration; C_{max}: Maximum drug concentration; $t_{1/2\beta}$: Elimination half-life; $AUC_{(0-\infty)}$: Area under the curve from zero to infinity; Vz: Volume of distribution; Cl: Total body clearance; MRT: Mean residence time.

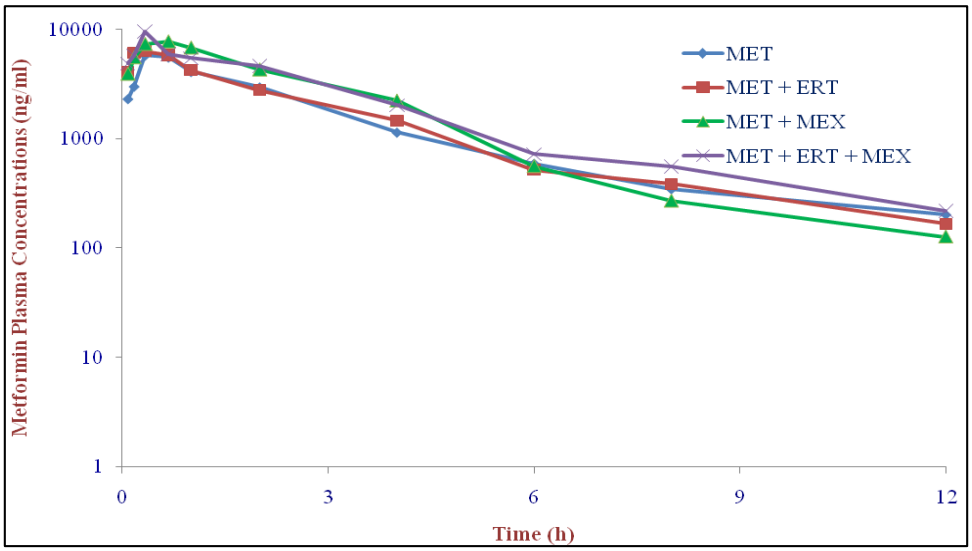

Fig 1: Semi logarithmic plot of metformin plasma concentration following single dose administration (100 mg/kg, p.o) alone and combination with erlotinib (30 mg/kg, p.o), and/or meloxicam (20 mg/kg, i.p) in male SCID mice.

4. Discussion

The Carcinogenic conditions are observed at old age and are involved with many other complication pertaining to metabolic disorder like diabetes. The prevalence and incidence of diabetes is increasing in most populations and it has been documented that people with diabetes are at significantly higher risk for many forms of cancer. In such condition combination therapy is envisaged, which may lead to produce unpredictable therapeutic outcome due to their interaction. Hence, to treat such complicated conditions, drug

therapy with mTOR inhibitors, EGFR inhibitors and COX-2 inhibitors may be used to produce relief from symptoms. Looking to the application of such combination therapy, the study was planned to evaluate impact of erlotinib and meloxicam administration on pharmacokinetics of metformin in SCID mice.

The mean value of calculated Tmax remained lower in metformin with erlotinib treated animals and all three drugs together treatment group compared to metformin with meloxicam and metformin alone treatment groups. The calculated Cmax of metformin was observed higher in metformin with meloxicam and all three drugs together group compared to other treatment groups. The $AUC_{(0-\infty)}$ was significantly ($p<0.01$) higher in metformin with meloxicam treated group and all three drugs together ($p<0.01$) compared to meloxicam alone treated group. The drug clearance rate was also observed significantly lower in treatment group of metformin with meloxicam ($p<0.05$) and all three drugs together ($p<0.05$) compared to meloxicam alone treatment group. The volume of distribution was also significantly lower in all treatment groups compared to that of metformin alone treated group. The half-life of metformin when given with meloxicam was found to be significantly lower compared to metformin alone treatment group.

The significant increase in values of C_{max} and $AUC_{(0-\infty)}$ was observed when metformin administered along with erlotinib and all three drugs together in present study which indicates that combinational therapy with metformin along with erlotinib and meloxicam increases concentration of metformin over a time. Similar findings have also been reported that furosemide, nifedipine and cimetidine have been found to increase the Cmax and AUC of metformin [25]. The higher value of $AUC_{(0-\infty)}$ in metformin with meloxicam treated animals and metformin with erlotinib and meloxicam treated animals indicate that vast area of body is covered by metformin concentration. This significant change in $AUC_{(0-\infty)}$ of metformin can be correlated with other pharmacokinetic parameter like volume of distribution, half-life and clearance. The volume of distribution in present study has also been found significantly lower in treatment group of metformin with erlotinib, metformin with meloxicam and all three drugs together. This finding is suggestive of alteration in metformin transport and /or cellular uptake when administered in combination with other drugs. Similar finding have been observed that drugs like tyrosin kinase inhibitor (Imatinib, dasatinib, nilotinib, gefitinib, erlotinib, sunitinib, lapatinib and soratinib) are competitive inhibitor of metformin uptake through organic cation transporters (OCT) and decrease the volume of distribution at various level [26]. The calculated clearance rate was also observed significantly lower in treatment group of metformin with meloxicam ($p<0.01$) and all three drugs together ($p<0.01$) compared to metformin alone treatment group, which suggests that drug is slowly eliminated from body. This significant decrease in clearance of metformin when given in combination with meloxicam and all three drugs together might be due to alteration in renal clearance of metformin when administered with other drugs. Similar report by Rani *et al*. [27] indicating that metformin clearance is significantly decrease when given in combination with trandolapril. The decrease in clearance of metformin when given in combination with meloxicam might also be due to reduce clearance of drug through kidney as a result of decreased blood flow to kidney in presence of meloxicam [28].

5. Conclusions

Metformin pharmacokinetic profile is altered when administered in combination with erlotinib and/or meloxicam in SCID mice. However, study on clinical pharmacokinetic interaction of these drugs is required to evaluate interaction in human patients

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