International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

A Study on Effect of Food on Pharmacokinetics of Clindamycin: A Research

Akshay S. Kshirsagar[1], Vipul M. Patil[2], Dr. Sachinkumar Patil (PhD)[3]

[1, 2]M. Pharmacy

Abstract: ***Clindamycin formulations (capsules, administered orally were studied in twenty adult indian human males) in fed and fasting conditions. Bioavailability, pharmacokinetics and recovery were determined for each subject. A standard dose 150mg was used in study. The mean pharmacokinetics parameters calculated for each subject my SAS software (Version 9.4). In pharmacokinetics parameters we calculated Cmax and AUC(0-t). These mean values are lower than those reported in the literature for healthy volunteers, and the variation between patients is also larger. The blood concentration-time curves for the tablets were very scattered, which was far less the case for the capsules. The maximum blood concentration (Cmax) for fed study were very low than the fasting study. The time at Cmax were more for fed condition as compare to fasting condition. The mean absorption rates found for the two study did differ from those found in healthy volunteers, clindamycin being absorbed significantly more slowly in fed condition than fasting condition.***

Keywords: Clindamycin, Bioavailability, metabolism, pharmacokinetics

1. Introduction

The bioavailability of the medication is normally assessed in a fasting condition to the stay away from the confounded obstruction with food. Regardless, research the effects of meal on bioavailability, as the medications are every now and again controlled after food confirmation, and adaptation of bioavailability achieved by food, in the event that it happens, may cause critical changes in clinical reaction. Solid meal have been exhibit to reduce stomach releasing rate, and gastrointestinal motility developments inside seeing food. Since most medications are consumed from the small digestive system, deferred stomach discharging may postpone the beginning and diminish the pace of ingestion. Food might decrease the point of retention of drug that are temperamental at low PH. Then again, drawn out maintenance in the stomach might build the point of a controlled medication that is in arrangement when the long run passes into the small digestive tract and may along these lines increment the point of ingestion. In a strong gastrointestinal framework, the residence of food in the structure triggers the attending of stomach destructive and narrowing of the muscles of the stomach. In a sound gastrointestinal framework, the occurrence of meal in the structure triggers the appearance of stomach destructive and pressure of the muscles of GIT. Extending the stomach's affectability to the occurrence in food ensures that preparing progresses quickly. This survey incorporates investigation to analyse effect of meal utilization upon to pharmacokinetics of Clindamycin, taking a gander at AUC (district undergoing the plasma centre versus time profile), Cmax (top plasma level), and Tmax (time to top plasma level) at same piece of Clindamycin, after ingestion in both avoided and dealt with state.[1] effect of food and without food on drug showing in figure no.1.0.

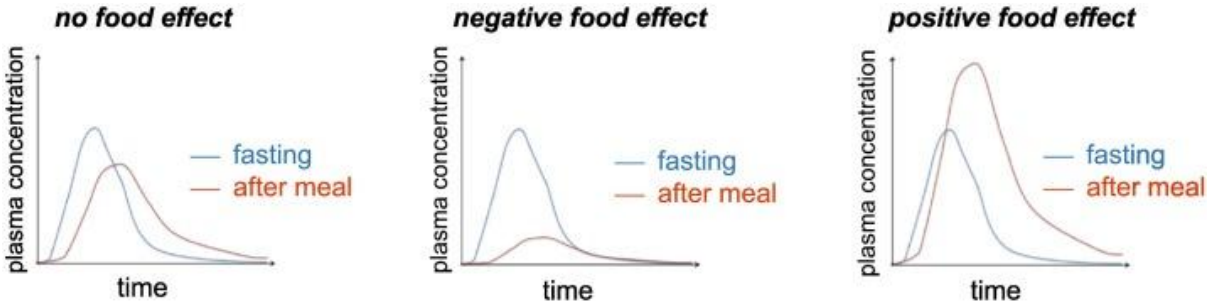

Figure 1: Food effect on absorption

Exactly when two subtleties of comparable drug or two medicine things are attested bioequivalent, it acknowledged that they should give the extremely therapeutic effect. For the present circumstance, by far most unravel that they can be used then again. Two prescription things are seen as medication reciprocals if they contain vague proportions of a comparative unique fixing. Two prescriptions are perceived as medication choices as opposed to each other if both contain an unclear accommodating moiety, yet not actually in a comparative total or estimation structure or as a comparable salt or ester. Two medicine things should be bioequivalent on the off chance that they are drug reciprocals (i.e., near portion structures made, possibly, by different makers) or medication choices (i.e., unmistakable portion structures) and if their rates and levels of osmosis don't show a basic differentiation to which the unique fixing or dynamic moiety in drug partners or medication decisions become open at the area of action when coordinated at comparable molar piece under relative situation in an appropriately arranged audit.

When an inventive (or brand-name) drug thing is going off patent, drug or nonexclusive associations may record a contracted new medicine application (ANDA) for ordinary support. Ordinary prescription things are described as medicine things that are vague from an innovative (brand-name) drug which is the subject of an embraced NDA as to dynamic ingredient(s), course of association, estimation construction, strength, and conditions of use. Since ANDA sections for nonexclusive applications don't require broadened clinical appraisal of the ordinary meds being examined the expense of generics are normally much low the firsts. All around, it is greater 20% of the expense of the brand-name firsts. In 1984, the (FDA) was supported to underwrite traditional medicine things under the medication Price Competition and Patent Term Restoration Act. The justification behind existing is to improve more reasonable, safe, and also satisfactory generics open to by and large populace after the pass of patent protection of exorbitant brand-name drugs. For support of nonexclusive medicine things, the FDA requires that evidence of ordinary bioequivalence in drug maintenance be given through the direct of bioavailability and bioequivalence considers. Bioavailability is portrayed as relative proportion of medicine from a controlled portion which go for the central stream and the cost at which the prescription appears in major spread. The bioavailability studies have been concluded by assessing the centralization of the prescription in plasma or blood behind association of medication following key show of studies and recorded as time goes on. The central show is valuable for clinical primers in the early prescription headway, and the data got are used in following bioequivalence looks at. Bioequivalence studies have been done to perceive two medication things containing a comparable unique substance. One prescription framed into two unmistakable definitions if they reveal happen remedially indistinguishable from one another happen considered replaceable.

Meal could be change the pace of assimilation and pharmacokinetics of the medications regulated orally. The FDA need the assurance of food impact for most medications. Pharmacokinetics (PK) is pivotal to the accomplishment of this sort of study. Draw in a pharmacokinetics during convention improvement to devise an appropriate PK blood inspecting plan on account of the likelihood that meal can change the time direction of plasma medication fixations. The full PK profile should be created dependent on a sufficient testing plan or the review might neglect to meeting its goal of deciding a food impact. Given the horde of food consequences for drug retention and bioavailability, the almost difficult to foresee what food will mean for the pharmacokinetics of likely medication without really having the information. Subsequently, a food impact bioavailability study is dominant to sufficiently portray what food will mean for a medication's pharmacokinetics.

2. Case Study (Method)

Clinical study of Clindamycin:
During this evaluation, the criteria of the ICH (Step 5), the 'Direction for Good Clinical Practices (GCP)'150, and the Declaration of Helsinki were followed (Scotland, October 2000).

Screening of Volunteer In 18 solid, male volunteers, a randomized, open mark, 2-way hybrid review was conducted. Before medication was given out, the screening assent and the research assent were obtained independently. The clinical data of the subjects was then stored, and real examination was guided. To identify eligibility, researchers employed a clinical wellbeing evaluation that comprised an individual meeting, a full actual assessment (BP, beat, weight, temperature, and respiration rate); and research centre testing that included a total platelet count and pee examination. Testing was completed. (refer annexure 10.4) the research center's quality was considerably above/below the reference range, or if all tests has not been completed, subjects were eliminated. Furthermore, the clinical unit agents evaluated the research Centre facts prior to enrolling the individuals. to gain support, subjects were invented.

Check-in of Volunteer: Participants was admitted to the hospital 12 hours before to treatment and were discharged 48 hours afterwards. During check-in body baggage and frisking was done.

Dosing of Subject: Subject received single oral portions (150 mg Clindamycin) under fasting or after a high fat meal following overnight fast of at least 12 hours. Washout periods of many weeks were maintained between the medications. Four hours after treatment, all individuals were given normalised supper, followed by normalised lunches seven and eleven hours later. The criteria were developed in response to global food cooperation research requirement

Collection and processing of blood sample: Blood samples (1x 3 mL) were taken at the following times during the intravenous course using heparinized dispensable needles: Pre-portion and after drug organisation at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0, and 24.0 hours Following the collection of blood tests from each participant, blood was collected in vacutainers containing EDTA as an anticoagulant and centrifuged at 3000 rpm for 15 minutes before being divided into two aliquots. The isolated plasma tests were maintained at or below - 20^{o}C until they were analysed. Clindamycin levels in plasma was calculated using a HPLC method.

Check-out of subject Basic symptoms, ECG, and research facility constraints were not appropriately described throughout the hospitalisation period. order to measure abstract prosperity, people were told to look unpleasant occurrences in a non-driving manner and to characterise any unfriendly circumstances that happened shortly. A score was calculated based on severity of problem and likelihood that it was caused by drug in question. Any medicine administered during the examination was recorded.

The following pharmacokinetic parameters for clindamycin were calculated:

Cmax: Uninterrupted maximum estimated plasma focus during the whole examining duration, computed directly from plasma fixation vs time bending test data.

Tmax: The plasma focus is thought to be at its most intense at Tmax (Cmax). If most severe worth happens at more than

one point in a period Tmax is defined as main point having this worth in every period.

AUC0-t: Area under plasma focus vs. time bend from dosing season to last measurable fixation season, as determined by the direct trapezoidal technique.

Cmax and Tmax were computed directly from the individual plasma concentration versus time curves that were produced. AUC was calculated using the trapezoidal method from time 0 (gauge) - 24 hours,

$$\mathbf{AUC_{0-\infty} = AUC_{0-24} + (C_{24/kel})}$$

where C_{24} is the concentration measured after 24 hours, was used extrapolate AUC from baseline to infinity ($AUC_{0-\infty}$).

Geometric implications of pharmacokinetic parameters Cmax and AUC_{0-t} were used to determined the formulation ratios. Point estimates was used arrive at these statistics. For the log transformed pharmacokinetic parameters [Cmax, and AUC_{0-t}], a 90 percent confidence interval for the ratio of study formulations was created using the ANOVA result from the log-transformed data analysis. The study formulation equivalence was then calculated using the 90 percent confidence interval. The medicines are stated to be bio-similar if the point gauge of mathematical mean proportion and certainty spans throughout the full log changed pharmacokinetic limits [Cmax and AUC0-t] for the range of 80-125 percent.

Precision & Accuracy: After six repetitions of standard arrangement were inserted into HPLC framework, the pinnacle space and RSD were determined. To assess procedure accuracy, six free tests for the two Clindamycin details were employed (intraday accuracy). In the same laboratory, the method's intermediate accuracy (inter-day precision) was assessed using two distinct analysts, systems, and days. The recommended approach was put to the test using recovery trials. At three levels, identical solutions for each formulation were tested for % recovery tests (50 percent, 100 percent, and 150 percent). According to label claim, the assay results were reported as a % of amount of Clindamycin found in the capsule formulations.
These arrangements were broken down for its rate pharmaceutical ingredient regarding name guarantee by a single investigator multiple times a single day and by another expert once a day for six days to determine the rate correctness of the strategy.

Robustness: Clindamycin retention time was determined after modest purposeful modifications in chromatographic conditions were performed at different levels: -1, 0, and +1.the ability to withstand or overcome adverse conditions or rigorous testing.

3. Results

Interpretation of AUC, Cmax
In statistical result we calculated the mean, Geomean, Median, Maximum, S.D., range of Cmax, Tmax, AUC, values, Kel, t1/2, Tlag which is all are this pharmacokinetics parameters.

This all statistical results calculated from SAS program and its version no. 9.4.

Statistic	Cmax (ng/Ml)	Tmax (h)	AUC (0-t) (ng*h/mL)	AUC (0-inf) (ng*h/mL)	Kel (1/h)	t1/2 (h)	T lag (h)
Mean	106.611	6.59	1594.680	2213.915	0.089	9.089	0.632
GeoMean	99.545	6.09	1409.668	1845.558	0.081	8.221	0.542
Median	101.403	6.00	1628.450	1886.510	0.079	7.811	0.500
Minimum	52.630	2.02	600.403	716.895	0.025	4.033	0.000
Maximum	192.161	12.00	3319.360	5702.810	0.172	27.544	1.500
S.D.	40.32	2.48	778.96	1405.16	0.04	5.08	0.34
Range	139.53	9.98	2718.96	4985.92	0.15	23.51	1.50
%CV	37.8	37.6	48.8	63.5	40.8	55.9	53.4
N	19	19	19	19	19	19	19

Following summary table shows a Descriptive Statistics of Pharmacokinetic Variables of fasting study.

Statistic	Cmax (ng/mL)	Tmax (h)	AUC (0-t) (ng*h/mL)	AUC (0-inf) (ng*h/mL)	Kel (1/h)	t1/2 (h)	T lag (h)
Mean	262.945	2.89	2382.655	3048.791	0.102	9.080	0.403
Geo Mean	245.883	2.69	2084.615	2486.244	0.090	7.670	0.364
Median	236.135	3.00	1951.515	2140.965	0.101	6.939	0.250
Minimum	109.189	1.50	924.462	1015.220	0.027	3.941	0.000
Maximum	490.665	6.00	5195.390	8873.310	0.176	25.977	1.000
S.D.	100.40	1.17	1287.33	2201.47	0.04	6.46	0.26
Range	381.48	4.50	4270.93	7858.09	0.15	22.04	1.00
%CV	38.2	40.5	54.0	72.2	43.0	71.1	64.4
N	18	18	18	18	18	18	18

Following table shows summary of the Comparative Bioavailability Data for fed and fasting conditions. In the table we can easily compare bioavailability of both condition.

Parameter (Log transformed)	Geo-Mean ratio (fed /fasting)	90% Confidence limit (0.8-1.25)		Conclusion (fed vs fasting)
		Lower	Upper	
Cmax	0.526	0.4819	0.5736	Not equivalent
AUC(0-t)	0.883	0.8150	0.9551	Equivalent

The following table shows summary comparative data of feds and fasting studies. The table shows the comparative pharmacokinetics parameter of all subjects with respective fed and fasting condition.

PK Parameters	Fed	Fasting
Cmax (ng/mL) Mean±SD	106.611+40.32	262.945+100.40
AUC(0-t) (ng*h/mL) Geo mean±SD	1409.668+778.96	2084.615+1287.33
AUC(0-inf) (ng*h/mL) Geomean±SD	1845.558+1405.16	2486.244+2201.47
Tmax(h) Median±SD	6.00+2.48	3.00+1.17
Kel(1/h) Mean±SD	0.091+0.03	0.102+0.04
t1/2 Mean±SD	9.089+5.08	9.080+6.46
T lag (h) Mean±SD	0.632+0.34	0.403+0.26

4. Conclusions

The study's main goal was to examine how meals affected Clindamycin pharmacokinetics. Clindamycin's primary bioavailability & bioequivalence measurements in both fasting & fed conditions were Cmax, Tmax, and AUC. Because the fed/fasting Clindamycin 90 percent CI did not fall within the permitted range, it's conceivable that rate of systemic Clindamycin exposure does not meet the claim of bioequivalence to fasting and fed therapy (80, 125).

According to findings of this investigation, all of the pharmacokinetic parameters both regimens were significantly different. The extent to systemic exposure for Clindamycin was impacted by delay in Clindamycin absorption in presence of food in fed condition, suggesting that the delay in Clindamycin absorption in the presence of food influenced extent of systemic exposure for Clindamycin. No major adverse effects were recorded by any of subject in period of study. There were just two adverse events both of which mild and unrelated to the study medication. The AEs that were reported, according to the study medical expert, were related to the sample technique, were self-limiting, and did not require treatment. The individual's vital indicators were constant throughout the study. The data presented here will be crucial in identifying the most effective dosing for future oral Clindamycin clinical trials.

References

[1] Prentis RA., Lis Y, and Walker SR.: Pharmaceutical innovation by seven uk-owned pharmaceutical companies British Journal of Clinical Pharmacology. 25: 387–396, 1964–1985, 1988.

[2] Haynes, R., Sackett, D. & Gibson, E. Improvements of medication compliance in uncontrolled hypertension. Lancet, 1256-1268, 1976.

[3] Routledge, P. A. Clinical pharmacology and the art of bespoke prescribing. British Journal of Clinical Pharmacology, 26, 339-347, 1988.

[4] Melrose, D. Bitter pills: medicines and the third world poor. Oxford U.K.: Oxfam, 1982.

[5] Florence AT, Salole EG. The clinical relevance of the formulation of medicines. In: Lawson DH, Richards RHE, eds. Clinical pharmacy and hospital drug management. London: Chapman and Hall,:1-37, 1982.

[6] Parsons RL, David JA., Gastrointestinal disease and drug absorption. In: Prescott LF, Nimmo WS, eds. Drug absorption. New York: Adis Press, 262-77, 1981.

[7] Wahlin-Boll, E.. Mclander. A.. Sartor. 6. & Scherten, B. Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects. Europe. Journal of Clinical Pharmacology 18, 279-283, 1980.

[8] Sartor, G., Lundquist, I., Melander, A., Schersten, B. & Wahlin-Boll. E. lmprovcd cffect of glibenclaimide on administration before breakfast. Europe. Journal of Clinical Pharmacology, 21. 403-408, 1982.

[9] Cummins CL, Wu CY and Benet LZ. Sex-related differences in the clearance of cytochrome P450 3A4 substrates may be caused by Pglycoprotein. Clinical Pharmacology and Therapeutics.;72: 474–89, 2002.

[10] Dietrich R, Brausse R, Bautz A and Diletti E. Validation of the in-vitro dissolution method used for the new sustained-release theophylline pellet formulation. Arzneimittelforschung/ Drug Research. 38:1220, 1988.

[11] Diletti E, Hauschke D and Steinijans VW. Sample size determination for bioequivalence assessment by means of confidence intervals. International Journal of Clinical Pharmacology, Therapy and Toxicology.;29:1–8, 1991.