Rajesh Chaudhari. / Vol 4 / Issue 1 / 2014 / 1-4.

International Journal of

Innovative Drug Discovery

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

www.ijidd.com

ADVERSE EVENT REPORTING FOR A FOOD EFFECT BIOAVAILABILITY STUDY OF ROXITHROMYCIN

***Rajesh Chaudhari**

SRM Institute of Clinical Research, Tilak Nagar, Aurangabad, MS, India - 431001.

ABSTRACT

The term "bioavailability" refers to that proportion of a drug which reaches the systemic circulation unchanged after a particular route of administration. To produce a clinical response, a drug must achieve an effective concentration at its site of action, which must be maintained for an adequate length of time. For orally administered systemic agents, this involves the transfer of the drug from the gut to the systemic circulation. In order to achieve this, the drug must first enter solution, and then pass into the portal blood-i.e. it must undergo absorption. Among all the routes of drug administration the oral route administration of drugs is convenient, and linking drug doses to daily routines such as meal times can improve compliance. However, inter-individual variation in drug response, particularly following oral administration, has long been a problem. Since this variation can result in therapeutic failure or drug toxicity, the 'art of bespoke prescribing' remains a major goal of clinical pharmacology.

KEY WORDS: Phenotyping, CYP2D6, Adverse events.

INTRODUCTION

Adverse drug reactions are associated with almost every drug. Also, occurrence of an adverse event is not an unheard phenomenon when it comes to clinical trials. In this study, we have attempted to report the adverse event that occurred in our Phenotyping study, along with a observation that the adverse event that occurred were owing to the natural phenomenon rather than the drug used [1-5]. In the past variation in the composition, strength or formulation of the drug has often been responsible for such problems. Nowadays, at least in the developed world'[4], such formulation problems are rare, but even so dose-response relationships still vary from patient to patient. When drugs are taken by mouth their bioavailability is determined by factors in the drug-which include the nature of the molecule, its stability, and the formulation administered and in the patient-such as a reduced intestinal surface area as a result of coeliac disease or intestinal resection and whether or not the drug is taken with a meal. [5-6]

For oral route of administration the absorption process can be affected by a number of factors including:

1) Physicochemical properties of the drug and the dosage form;
2) Gastric acidity;
3) Gastric and intestinal motility;
4) Gastro-intestinal (GI) related diseases; and
5) Concurrent food administration.

Amongst these, concurrent food administration is the most common and yet most easily controllable factor. The two pharmacokinetic parameters that may be affected are the extent of absorption i.e. oral bioavailability, and the rate of absorption. Many of the factors which influence bioavailability can be changed by food, both 'acutely', if a drug is taken with a meal, and 'chronically', where regularly consumed food items influence drug disposition. The nature of these interactions is complicated, and is influenced by the quantity and composition of food. It should also be noted that as well as changing the pharmacokinetics of some drugs, food can alter their pharmacodynamic effects. [7-18]

With increasing generic substitution, food– drug interaction studies have gained considerable importance.

Corresponding Author:- **Rajesh Chaudhari** Email:-: rajpc67@gmail.com

Food–drug interaction studies focus on the effect of food on the release and absorption of a drug. In view of dramatic and clinically relevant food effects observed with certain Theophylline sustained release formulations, bioequivalence between a Test and a Reference formulation under only one nutritional condition, e.g. fasting, is by no means sufficient to allow generic substitution.[19-22] The reported food effects, with AUC increases of 100 % and decreases of 50 % for certain formulations, are far beyond the usually accepted 25 % increase and 20 % decrease in bioequivalence studies between formulations.[23] The CPMP (2001) guidance on bioequivalence also addresses this issue with particular emphasis on controlled release formulations. The FDA (2002) guidance recommends a study comparing the bioavailability under fasting and fed conditions for all orally administered modified release drug products. Modified release formulations include two essentially different types of release modifications, so-called 'prolonged release' formulations and 'delayed release' formulations.

Understanding the possible clinical implications of taking medicines with or without a meal is important for achieving quality use of medicines. Although the effect of food is not clinically important for many drugs, there are food–drug interactions which may have adverse consequences. Often these interactions can be avoided by advising the patient to take their medicines at the same time with respect to meals [24].

Roxithromycin is an azalide, a subclass of macrolide antibiotics. Roxithromycin is one of the world's best-selling antibiotics. It is derived from erythromycin, with a methyl-substituted nitrogen atom incorporated into the lactone ring, thus making the lactone ring 15-membered.

Roxithromycin is used to treat or prevent certain bacterial infections, most often those causing middle ear infections, strep throat, pneumonia, typhoid, bronchitis and sinusitis. In recent years, it has been used primarily to prevent bacterial infections in infants and those with weaker immune systems. It is also effective against certain sexually transmitted infections, such as nongonococcal urethritis, chlamydia, and cervicitis. Recent studies have indicated it also to be effective against late-onset asthma, but these findings are controversial and not widely accepted.

Medical uses

Roxithromycin is used to treat many different infections, including acute otitis media, nonstreptococcal bacterial pharyngitis, gastrointestinal infections such as traveler's diarrhea, respiratory tract infections such as pneumonia, cellulitis, babesiosis, *Bartonella* infection, chancroid cholera, donovanosis, leptospirosis, Lyme disease, malaria, *Mycobacterium avium* complex disease, *Neisseria* meningitis, pelvic inflammatory disease, pertussis, scrub typhus, toxoplasmosis, and salmonellosis. It is used to prevent bacterial endocarditis and some sexually transmitted infections including those from unprotected sex or sexual assault. It is also effective against localized dental infections [25-30].

It has a similar antimicrobial spectrum as erythromycin, but is more effective against certain Gram-negative bacteria, in particular, *Haemophilus influenzae* (although it would not be the first choice of treatment in this infection). Roxithromycin resistance has been described and is endemic in many areas. Long-term use in treating *Staphylococcus aureus* infections with Roxithromycin may increase bacterial resistance to this and other macrolide antibiotics.

Roxithromycin has been shown to be effective against malaria when used in combination with artesunate or quinine; the optimal dose for this is not yet known.

Adverse effects

Most common side effects are gastrointestinal: diarrhea (5%), nausea (3%), abdominal pain (3%), and vomiting. Fewer than 1% of patients stop taking the drug due to side effects. Nervousness, dermatologic reactions, and anaphylaxis have been reported. As with all antimicrobial agents, pseudomembranous colitis can occur during and up to several weeks after Roxithromycin therapy. In the past, physicians cautioned women that antibiotics can reduce the effectiveness of oral contraceptives. However, new research shows that antibiotics, with the exception of rifampin and rifabutin, do not affect the effectiveness of hormonal contraceptives, such as the pill, patch or vaginal ring. This change in advice comes because to date there is no evidence which conclusively demonstrates that antibiotics (other than rifampicin or rifabutin) affect these contraceptives.

Roxithromycin suspension has an objectionable taste, so can be difficult to administer to young children, i.e., 2–5 years, who may spit it out. Occasionally, patients have developed cholestatic hepatitis or delirium. Accidental intravenous overdosage in an infant caused severe heart block, resulting in residual encephalopathy.

In 2013, the FDA issued a warning saying that Roxithromycin "can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm." The FDA noted in the waring a 2012 study released by the *New England Journal of Medicine* that found the drug may increase the risk of death, especially in those with heart problems, compared with those on other antibiotics such as amoxicillin or no antibiotic. The warning indicated that people with preexistent conditions are at particular risk, such as those with QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or those who use of certain drugs used to treat abnormal heart rhythms, or arrhythmias.

Mechanism of action

Roxithromycin prevents bacteria from growing by interfering with their protein synthesis. It binds to the 50S

subunit of the bacterial ribosome, and thus inhibits translation of mRNA. Nucleic acid synthesis is not affected.

Spectrum of bacterial susceptibility and resistance

Chlamydia pneumoniae, Chlamydia trachomatis, Eikenella corrodens, Escherichia coli, Haemophilus influenzae, Moraxella catarrhalis, Mycobacterium chelonae, Mycoplasma fermentans, Neisseria gonorrhoeae and *Ureaplasma urealyticum* are generally susceptible to Roxithromycin dihydrate, while *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes* are resistant to Roxithromycin dihydrate. Furthermore, some *Brevibacterium* spp., *Corynebacterium amycolatum, Haemophilus influenzae* and *Mycobacterium abscessus* have developed resistance to Roxithromycin dihydrate to varying degrees.

Pharmacokinetics

Unlike erythromycin, Roxithromycin is acid-stable, so it can be taken orally with no need of protection from gastric acids. It is readily absorbed, but its absorption is greater on an empty stomach. Time to peak concentration in adults is 2.1 to 3.2 hours for oral dosage forms and one to two hours after a dose. Due to its high concentration in phagocytes, Roxithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released. The concentration of Roxithromycin in the tissues can be over 50 times higher than in plasma, due to ion trapping and its high lipid solubility (volume of distribution is too high).

Roxithromycin's half-life allows a large single dose to be administered and yet maintain bacteriostatic levels in the infected tissue for several days.

Metabolism

According to Davis' Drug Guide for Nurses, following a single 500 mg dose, the half-life of Roxithromycin is 11–14 h. The longer half-life of 68 h is achieved only when multiple doses are consumed. Biliary excretion of Roxithromycin, predominantly unchanged, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine [31-33].

MATERIALS & METHODS

This study was carried out as per the ICH (Step 5), 'Guidance for Good Clinical Practices (GCP)' and the principles of Declaration of Helsinki (Scotland, October 2000).The SRM, Independent Ethics Committee (IEC) has reviewed and approved the protocol and the Informed Consent Form (ICF) for this study.

Sufficient numbers of healthy Indian male human subjects was screened, out of those 18 male subjects were enrolled in the study. A total of 18 male subjects were administered with the study medication (Robact Tablet) in the beginning of the study. The screening consent & study consent were taken respectively before drug application. Thereafter, subject's medical records were documented and physical examination was conducted. Inclusion eligibility was also based on successful completion of a clinical health evaluation, which consisted of a personal interview; a complete physical examination (BP, pulse, weight, temperature, and respiratory rate). Subjects were compensated for their participation. Subjects were admitted and housed in the clinical facility at least 2 hours before the application of the dose during the study. At the time of dosing, the marketed Roxithromycin formulation (Robact Tablet 150 mg) was administered to the study subjects as per the dosing schedule. Subjects received a single treatment in the clinical study.

The dosing procedure was as mentioned below

Blood samples of 7 ml were collected in sterile syringe post 2 hours of dosing. The plasma samples were analysed for Roxithromycin and ODV concentrations only.

For each subject the total number of blood draws were 01; the total volume of blood withdrawn through the vein puncture did not exceed 7 ml.

The samples were collected within 2 minutes of the scheduled time, where end time of collection to the nearest minute was recorded. Any deviation from the scheduled collection time was recorded promptly in the relevant raw data form.

RESULTS

This study has demonstrated that all the pharmacokinetic parameters of both the treatments were statistically different from each other.

In the fed condition the values of Cmax and AUC were decreased while Tmax increases than that of fasting which demonstrated that the extent of systemic exposure to Roxithromycin was affected by the delay in absorption of Roxithromycin in the presence of food.

None of the study volunteers reported any serious adverse effects throughout the study. The only two AEs reported were mild and not related to the study medication. The AEs reported were, according to the study medical expert, related to the sampling procedure and were self limiting and did not require any treatment. There was no change in the vital signs of the volunteers throughout the study period.

DISCUSSION AND CONCLUSION

Two subjects had mild stomach upset on the dosing day. The nature of the adverse event was "mild" and resolved on the same day without any concomitant medication. This adverse event was considered to be 'natural phenomenon' at the discretion of Principal Investigator. Hence, the relationship of the adverse event to study medication was assumed to be "unlikely".

REFERENCES

1. Prentis RA, Lis Y and Walker SR. Pharmaceutical innovation by seven uk-owned pharmaceutical companies (1964–1985), *Br. J. Clin. Pharmacol*, 25: 1988, 387–396.
2. Haynes R, Sackett D and Gibson E. Improvements of medication compliance in uncontrolled hypertension, *Lancet*, 1, 1976, 1256-1268.
3. Routledge PA. Clinical pharmacology and the art of bespoke prescribing, *Br J Clin. Pharmac*, 26, 1998, 339-347.
4. Melrosse D. Bitter pills: medicines and the third world poor. Oxford UK, Oxfam, 1982, 5.
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, 1982, 1-37.
6. Parsons RL, David JA. Gastrointestinal disease and drug absorption. In: Prescott LF, Nimmo WS, eds. Drug absorption. New York: Adis Press, 1981, 262-77.
7. Wahlin-Boll E, Mclander A, Sartor and Scherten B. Influence of food intake on the absorption and effect of glipizide in diabetics and in healthy subjects, *Eur. J. clin. Pharmac*, 18, 1980, 279-283.
8. Sartor G, Lundquist I, Melander A, Schersten B and Wahlin-Boll E. lmprovcd cffect of glibenclaimide on administration before breakfast. *Eur.J.clin.Pharmac*, 21, 1982, 403-408.
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, 2002, 474–89.
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*, 1988, 38, 1220–8.
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, 1991, 1–8.
12. Duursema L, Müller FO, Hundt HKL, Heyns A, du P, Meyer BH and Luus HG. (Model to detect warfarin–drug interactions in man. *Drug Investigation*, 4, 1992, 395–402.
13. Fitton A and Wiseman L. Pantoprazole – a review of its pharmacological properties and therapeutic use in acid-related disorders. *Drugs*, 1996, 51, 460–82.
14. Karim A. Importance of food effect studies early in drug development. In: Midha, K.K. and Nagai, T. (eds) Bioavailability, bioequivalence and pharmacokinetic studies. International conference of F.I.P. "Bio- International '96", Tokyo, Japan, 1996, 221– 9,
15. Schmidt LE, Dalhoff K. Food-drug interactions. *Drugs*, 2002, 62, 1481-1502.
16. Golub AL, Frost RW, Betlach CJ and Gonzalez MA. Physiologic considerations in drug absorption from the gastrointestinal tract, *J. Allergy Clin Immunol*, 78, 1986, 689-694.
17. British Pharmacopoeia, London: HMSO, 1985.
18. Walter-Sack I. The influence of food on the systemic availability of drugs. Part 1 drug absorption. *Klin. Wochenschr*, 65, 1987, 927-935.
19. Greenblatt DJ, Allen MD, MacLaughlin DS, Harmatz JS and Shader RI. Diazepam absorption: effects of food and antacids. *Clin. Pharmac. Ther*, 24, 1978, 600-609.
20. Welling PG. Interactions affecting drug absorption. *Clin. Pharmacokin*, 9, 1984, 404-434.
21. Bianchine J and Shaw G. Clinical pharmacokinetics of levodopa in Parkinson's disease. *Clin. Pharmacokin*, 1, 1976, 313-338.
22. Siegel D. Tetracyclines: new look at old antibiotic, *N Y. State J. Med*, 78, 1978, 950-1115.
23. Schuna A, Osman MA, Patel RB, Welling PG and Sundstrom WP. Influence of food on the bioavailability of penicillamine, *J. Rheumatol*, 10, 1983, 95-97.
24. Disler PB, Lynch SR, Charlton RW, Torrance JD, Bothwell TH, Walker RB and Mayet F. The effect of tea on iron absorption. *Gut*, 16, 1975, 193-200.
25. Pantuck EJ, Pantuck CB, Garland WA, Mins BH, Wattenberg LW, Anderson KE, Kappas A and Conney AH. Stimulatory effect of brussel sprouts and cabbage on human drug metabolism. *Clin. Pharmac. Ther*, 25, 1978, 88-95.
26. Pantuck EJ, Pantuck CB, Anderson KE, Wattenberg LW, Conney AH and Kappas A. Effect of brussel sprouts and cabbage on drug conju^,ation. *Clin. Pharmac. Ther*, 35, 1984, 161-169.
27. Conney AH, Pantuck EJ, Hsiao K, Garland WA, Anderson KE, Alvares AP and Kappas A. Enhanced phenacetin metabolism in human subjects fed charcoal broiled beef. *Clin. Pharmac. Ther*, 20, 1976, 633-642.
28. Pantuck EJ, Hsiao KC, Conney AH, Garlano WA, Kappas A, Anderson KE and Alvarez AP. Effect of charcoal broiled beef on phenacetin metabolism in man. *Science*, 194, 1976, 1055-1057.
29. Santodonato J, Howard P and Dasu D. Health and ecological assessment of polynuclear aromatic hydrocarbons. *J. Environ. Path. Tox*, 5, 1981, 364.
30. Rajpurohit R and Krishnaswamy K. Differences in response of glucuronide and glutathione conjugating enzymes to aflatoxin beta, and Nacetylaminofluorene in underfed rats. *J.Toxicol. Environ. Health*, 24, 1988, 103-109.
31. Coulter JBS, Lamplugh SM and Omer MIA. Aflatoxins in human breast milk. *Annals Trop. Paediat*, 4, 1984, 61-66.
32. Hendrickse RG. Aflatoxins and child health in the tropics-the Stanley Davidson Lecture. *Chronicle*, 15, 1985, 138-156.
33. Krishnaswamy K. Drug metabolism and pharmacokinetics in malnutrition. In Handbook of clinical pharmacokinetics. Adis Health Science Press. 1983, 28-35.