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Bioavailability study of Norfloxacin co-prescribed with some analgesics

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Abstract: The present paper aimed to study the effect of normal availability of norfloxacin in human beings. E.coli organism was used to determine the minimum inhibitory concentration of norfloxacin and in-vivo studies had been conducted on healthy human beings. Norfloxacin is a fluoroquinolone antibiotic, it's a new class and paved a way to overcome the power of resistance developed by bacteria, thus chosen for present in vivo drug interaction study. According to report there are lot of research had been performed on the interaction between various antibiotic, but very little work had been done related to antibiotic drug interaction. The in-vitro studies of interactions between norfloxacin and analgesics drugs have already been performed. The present study deals with in vivo interactions of norfloxacin and analgesics.
Key Words: Norfloxacin, Antibiotics, Analgesics, In-vivo studies, Drug-interaction, Pharmacokinetics.

1. Introduction

Broad-spectrum antibiotic refers to class of antibiotic with activity against a wide range of disease-causing bacteria. Norfloxacin is an oral broad-spectrum fluoroquinolone antibacterial agent used in the treatment of urinary tract infections [1-8]. It is also sometimes used to treat stomach infections and some other systematic infections. These ailments are more often and accompanied with pain, pyrexia, vitamin deficiency, malaria etc. as a result some analgesic, antipyretics, antimalarials and vitamins etc may be prescribed together with norfloxacin [9-14]. So to study the effect of co-administration of these analgesics with norfloxacin is advantageous and it's also affect the availability of norfloxacin. In the literature, the studies on interaction of norfloxacin antibiotics had been reported but very little attention had been given to drug-antibiotic interactions [15-21]. In vivo interaction studies were performed by employing biological assay method for norfloxacin using test organism E.coli. Minimum inhibitory concentration determined by serial dilution method and by double dilution method.

2. Experimental

2.1 Materials & Methods:

All the reagents used were of Analytical reagent grade. Nutrient broth medium, beaf extract, yeast extract, nutrient agar, sodium hydroxide. Authentic culture of E.Coli was used.

2.2 Preparation of stock solution:

The stock solutions of antibiotic were prepared aseptically by solubilizing in 0.1 N NaOH and then diluted with sterile water to get the final concentration of 640□g/ml and 1000 □g/ml. These were further diluted with distilled water to get final concentrations of 1, 10, 6.4, 64□g/ml.

3. Minimum Inhibitory Concentration determination:

Doubling dilution method:

A set of ten tubes numebered1-10 were prepared. Each containing 5ml of nutrient broth medium. To first tube 5 ml of standard antibiotic solution diluted with nutrient broth medium was mixed. From this tube 5ml of solution transferred to next tube & mixed. Similarly serial dilutions had been made from 2 to 10. All tubes were inoculated with a drop of broth culture of test organism. Test tubes incubated for 24 hrs at 37□C. Minimum concentration inhibiting the growth of microorganism was taken as the MIC against organism.

Table I: Determination of MIC of antibiotic by doubling dilution method

Test tube No.	1	2	3	4	5	6	7	8	9	10
Medium	5	5	5	5	5	5	5	5	5	5
Dilution	1/2	1/4	1/8	1/16	1/32	1/64	1/128	1/256	1/512	1/1024
Final concentration of antibiotic (μg/ml)	0.64	0.32	0.16	0.08	0.04	0.02	0.01	0.005	0.0025	0.00125

*This solution was prepared by diluting 1ml of standard solution (6.4μg/ml) of antibiotic with nutrient broth to make upto 5 ml giving final concentration as 1.28μg/ml)

4. In-vivo studies on human volunteers

Norfloxacin was administered alone and with analgin (300 mg), aspirin (300mg) and paracetamol (500 mg). Each of these test drugs to different set of volunteers and urine samples were collected and subjected to assay for norfloxacin content. Test drugs were administered in a single dose as normally prescribed. The assay of urine samples were performed by biological assay method for antibiotic by using doubling dilution method. The rate and extent of elimination and absorption of norfloxacin as well as its availability were calculated.

5. Results

The results of MIC determination were tabulated as table 3 and 4. The minimum inhibitory concentration had been observed between 0.03-0.04. The urinary excretion data of norfloxacin alone and in combination with analgin, aspirin, paracetamol given in table. Semi logarithmic plot of $1-x_u/x_u \infty$ Vs Time were plotted. Fig.1. had been plotted from which elimination rate constant K_E were calculated from slope obtained by applying regression analysis.

Table II: MIC of norfloxacin against E.Coli (serial dilution method)

Test tube No.	1	2	3	4	5	6	7	8	9	10
Concentration (□g/ml)	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01
Set I	-	-	-	-	-	-	-	+	+	+
Set II	-	-	-	-	-	-	-	+	+	+
Set III	-	-	-	-	-	-	-	+	+	+

Table III: MIC of norfloxacin against E.Coli (doubling dilution method)

Test tube No.	1	2	3	4	5	6	7	8	9	10
Concentration (□g/ml)	0.64	0.32	0.16	0.08	0.04	0.02	0.01	0.005	0.0025	0.00125
Set I	-	-	-	-	-	+	+	+	+	+
Set II	-	-	-	-	-	+	+	+	+	+
Set III	-	-	-	-	-	+	+	+	+	+

Table IV: Dose administered –400mg of Norfloxacin alone

S.No.	Time in hrs	Mean amount excreted in mg	SD	Cumulative amount excreted in mg	$1-x_u/x_u \infty$
1	1	16.20	1.64	16.20	0.8579
2	2	58	1.89	74.20	0.3493
3	3	21.120	1.52	95.32	0.1642
4	4	5.8	0.97	101.2	0.1139
5	5	5.02	1.61	106.14	0.0693
6	6	4.29	1.31	110.53	0.0308
7	7	3.517	0.85	114.047	0.00

Table V: Dose administered –400mg of Norfloxacin + 300mg of Analgin

S.No.	Time in hrs	Mean amount excreted in mg	SD	Cumulative amount excreted in mg	1-x_u/x_u □
1	1	7.936	0.238	7.936	0.8911
2	2	20.16	1.34	28.096	0.6144
3	3	33.60	0.567	61.696	0.1534
4	4	8.256	0.034	69.952	0.04018
5	5	1.587	1.82	71.539	0.01160
6	6	0.846	0.938	72.379	0.0068
7	7	0.502	0.256	72.881	0.00

Table VI: Dose administered –400mg of Norfloxacin +300mg Aspirin

S.No.	Time in hrs	Mean amount excreted in mg	SD	Cumulative amount excreted in mg	1-x_u/x_u □
1	1	32.00	0.892	32.00	0.7310
2	2	21.6	1.02	53.6	0.5495
3	3	52.8	0.026	106.4	0.1058
4	4	9.76	1.345	116.16	0.0238
5	5	1.2	0.678	117.36	0.0137
6	6	1.04	0.34	118.4	0.0050
7	7	0.6	0.028	119.0	0.00

Table VII: Dose administered –400mg of Norfloxacin +500mg Paracetamol

s.no.	Time in hrs	Mean amount excreted in mg	SD	Cumulative amount excreted in mg	1-x_u/x_u ∞
1	1	21.696	1.349	21.696	0.835
2	2	68.254	0.452	89.914	0.3228
3	3	20.624	0.068	110.538	0.1603
4	4	8.264	0.242	118.803	0.0975
5	5	5.29	1.098	124.012	0.0570
6	6	5.00	0.025	129.012	0.0294
7	7	2.63	1.692	131.642	0.00

6. Discussion

The norfloxacin's minimum inhibitory concentration for E.Coli was around 0.04□g/ml. In vivo studies with human volunteers were performed and urinary excretion data was used to study the interaction of norfloxacin and some analgesics aspirin, analgin and paracetamol as test drugs. The elimination rate in different cases were determined and shown in table V-VIII. The absorption rate constant {K_a (per hrs)}, and elimination rate constant {K_E (per hrs)} were found as shown in table.VIII.

Table VIII: Results obtained from urinary excretion data

S.No.	Combinations	$t_{1/2(in\ hrs)}$	$K_{E(per\ hrs)}$	$K_{a\ (per\ hrs)}$
1	Norfloxacin	1.8925	0.3661	0.3838
2	Norfloxacin +Analgin	1.5464	0.4490	0.6332
3	Norfloxacin +Aspirin	6.93	0.100	0.4222
4	Norfloxacin +Paracetamol	1.8056	0.3838	0.2303

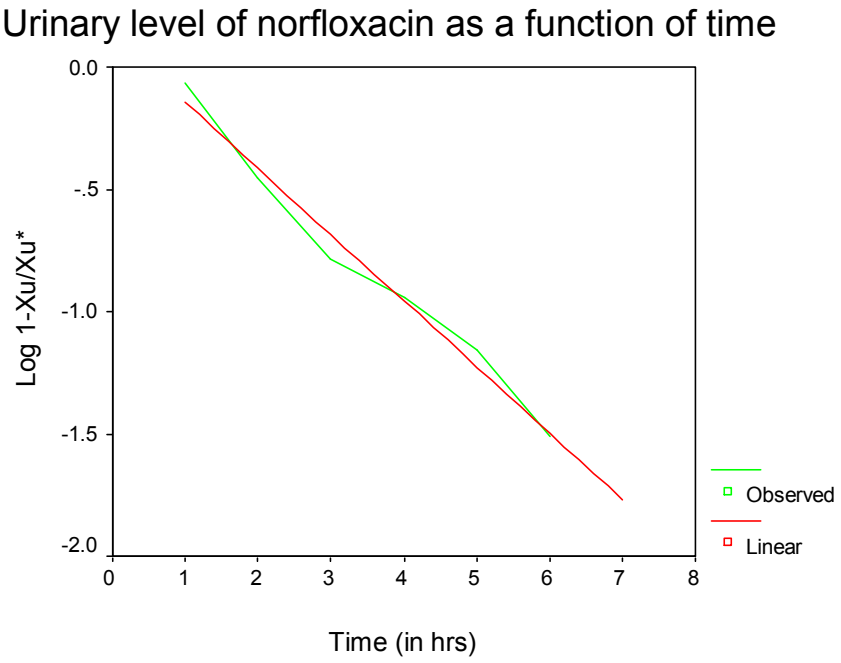

Fig.1 semilogarithmic Plot of Urinary Level of Norfloxacin as a function of Time

7. Conclusion

It's concluded that absorption, excretion kinetic and availability of norfloxacin is modified and altered in presence of each drug. From the in-vivo studies it is clear that in vitro findings could be correlated to in-vivo findings in this case. By in vivo studies one can ascertain how much increase and decrease in availability of norfloxacin occurs by these interactions. In cases where decrease in norfloxacin availability is observed, dose of norfloxacin antibiotic should be increases so as to obtain desirable action. When increase in norfloxacin availability is observed, dose of norfloxacin antibiotic should be decrease so as to obtain desirable action.

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