INFLUENCE OF TYPE AND NEUTRALISATION CAPACITY OF ANTACIDS ON DISSOLUTION RATE OF CIPROFLOXACIN AND MOXIFLOXACIN FROM TABLETS

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Abstract

Dissolution rate of two fluoroquinolone antibiotics (ciprofloxacin and moxifloxacin) was analysed in presence/absence of three antacid formulations. Disintegration time and neutralisation capacity of antacid tablets were also checked. Variation in disintegration time indicated the importance of this parameter, and allowed evaluation of the influence of postponed antacid-fluoroquinolone contact. The results obtained in this study showed decreased dissolution rate of fluoroquinolone antibiotics from tablets in simultaneous presence of antacids, regardless of their type and neutralisation capacity.

KEY WORDS: dissolution, neutralization capacity, ciprofloxacin, moxifloxacin, antacid, interaction

Introduction

Fluoroquinolones (FQ) are broad spectrum antibacterial agents which chemically, may be regarded as weak substituted heterocyclic amino acids (1). Fluoroquinolones are very efficient against aerobic Gram-negative microorganisms but less efficient against Gram-positive microorganisms (2,3). These drugs are extremely useful for the treatment of a variety of infections, including urinary tract infections (4), soft tissue infections (5), respiratory infections (6), bone-joint infections, typhoid fever, sexually transmitted diseases (7), prostatitis (8), community acquired pneumonia, acute bronchitis and sinusitis (9). Also, a relatively new approach to the rational design of antitumour agents has been introduced based on some new quinolone molecules that display a novel mode of action (10). Ciprofloxacin and moxifloxacin are members of fluoroquinolone family which belong to third and fourth generation of these drugs, respectively (11,12, 13). In clinical practice, fluoroquinolones are often administered concomitantly with other drugs which may contain metal ions. The presence of metal ions from *e.g.* metal based antacids may significantly affect the activity of quinolones since they can readily bind several divalent or trivalent metal ions (14). Complexation alters solubility, lipophilicity, antimicrobial activity and protein binding capacity of quinolones. Solubility of all ionic quinolone complexes is much greater than that of molecular complexes which are only sparingly soluble (15).

Some metal–quinolone complexes show antimicrobial activity comparable to that or free quinolone but in some cases the activity is increased or lowered. Mg^{2+} and Al^{3+} were found to decrease the activity of quinolones (14).

Therefore, the aim of this study was to:

- √ determine disintegration time and neutralization capacity of tablets containing antacids,
- √ evaluate the influence of certain antacids on dissolution rate of fluoroquinolones during simultaneous administration,
- √ determine dissolution rate of fluoroquinolone formulations (ciprofloxacin and moxifloxacin tablets) tested alone or in combination with antacids, and on the basis of the results obtained evaluate the influence of antacids, concerning their neutralization capacity, on dissolution rate,
- √ evaluate the influence of postponed antacid-fluoroquinolone contact in dissolution media on dissolution rate of ciprofloxacin and moxifloxacin tablets.

Materials and Methods

Reagents

The used reagents were all of analytical grade, unless otherwise stated. Ciprofloxacin hydrochloride monohydrate and moxifloxacin hydrochloride working standards were obtained from Merck (Darmstadt, Germany) and Bayer (Zürich, Switzerland), respectively. Hydrochloric acid 37% was obtained from by J.T. Baker (Deventer, Holland) and hydrochloric acid and sodium hydroxide titrimietric solutions (1,0 mol/dm^3) from Riedel-de Haën (Seelze-Hanover, Germany)

Tablet formulations

Three tablet formulations containing antacids were used. These antacid samples are marked as "M" (labelled strength: 333,3 mg $Al(OH)_3$ and 158,4 mg MgO), "G" (labelled strength: 450 mg $Al(OH)_3$, $MgCO_3$ jelly and 300 mg $Mg(OH)_2$), "R" (labelled strength: 500 mg hydrotalcite). For the fluoroquinolone antibiotics two tablet formulations were used: ciprofloxacin (labelled strength: 500 mg) and moxifloxacin (labelled strength: 400 mg).

Disintegration testing

The following disintegration test was performed; in each of six tubes, one tablet is placed. The assembly was suspended in the 1 litre beaker, containing 0,1 mol/dm^3 HCl, and operated (without disks). A suitable device maintained temperature of the liquid at 37°±0,5°C. The test was provided using Pharma Test disintegration tester Type PTZ (Pharma Test, Hainburg, Germany).

Determination of neutralization capacity

Ten tablets containing antacid were weighed and the average tablet weight was determined. The tablets were ground to a fine powder, mixed to uniformity. The quantity of it, equivalent to the average tablet weight, was transferred to a 250 cm^3 beaker, diluted in 50 cm^3 of water and mixed on magnetic stirrer for two minutes (200 rpm). 50 cm^3 of 1,0 mol/dm^3 HCl titrimietric solution (Riedel-de Haën, Seelze-Hanover, Germany) was added after mixing. After the addition of the acid the mixing procedure continued (200 rpm), accurately timed, for 10 minutes. Excess hydrochloric acid was titrated with 1,0 mol/dm^3 NaOH titrimietric solution (Riedel-de Haën, Seelze-Hanover, Germany) to attain pH 3,5 stable for 15 seconds. The obtained result is expressed in mEq of acid neutralised/per tablet.

In vitro dissolution assay

The dissolution tests of ciprofloxacin and moxifloxa-

cin coated tablets (n=6) were performed using USP apparatus 2 (n=6), Van Kel VK 7010 dissolution tester, at a stirring speed of 50 rpm (Van Kel, Cary, NC, USA). Dissolution profiles were determined at 37°±0,5°C in 900 cm^3 of 0,1 mol/dm^3 hydrochloric acid solution, pH=1,0. The paddle was positioned to extend to exactly 2,5 cm above the flask bottom.

Samples aliquots (5 cm^3) were collected using graduated syringe after 30 minutes. Prior to use, the dissolution medium was equilibrated at 37°C overnight to deareate medium. The suitability of the paddle apparatus was checked using the USP prednisone and salicylic acid calibrators -calibrators for system suitability test of basket and paddle dissolution apparatus (16). One tablet of the corresponding quinolone (ciprofloxacin or moxifloxacin) was placed in each filled flask (6 tablets per run) when establishing the dissolution profiles of quinolones in the absence of cations. These profiles were used to generate reference profile. To evaluate the influence of the different cations on the quinolone dissolution kinetics, the corresponding cation preparation was added to each flask at the same time as the quinolone formulation.

These samples were filtered using a "blue ribbon paper-391" (Munktell & Filtrak GmbH, Bärenstein, Germany) and quantified by UV/VIS spectrophotometric analysis (Shimadzu UV-1700, Kyoto, Japan).

Standard curves of absorbance versus concentration (in eight points) were constructed using solutions of:

◊ ciprofloxacin hydrochloride monohydrate (dissolution medium- 0,1 mol/dm^3 HCl, pH=1,0; previously degassed, ranging in concentration from 0,000075 mg/cm^3 to 0,015 mg/ cm^3; ($y = 120{,}510366x + 0{,}015705$; $r^2 = 0{,}998524$). UV absorbance of each standard solution was measured spectrophotometrically at 276 nm.

◊ moxifloxacin hydrochloride (dissolution medium- 0,1 mol/dm^3 HCl, pH=1,0; previously degassed, ranging in concentration from 0,0002 mg/ml do 0,04 mg/ cm^3; ($y=100{,}084681x + 0{,}009209$; $r^2=0{,}999813$). UV absorbance of each standard solution was measured spectrophotometrically at 295 nm.

Absorbance versus concentration plots were linear over these concentration ranges and were used to determine percent of drug dissolved in the dissolution experiments.

Results and Discussion

The results of disintegration testing are summarised in Table 1, neutralisation capacity determination in Table 2, and *in vitro* dissolution assay in Tables 3-4 (which show the amount of the dissolved drug-ciprofloxacin or moxifloxacin without/with antacid addition).

Values of dissolved moxifloxacin exceeding 100 % are well within the deviation range for content uniformity allowed for solid preparations by both US and European Pharmacopoeias (±10%) (17, 18).

Antacid formulation	Disintegration time
"M"	> 2 hours
"G"	≤ 7 minutes
"R"	≤ 40 seconds,

TABLE 1. Disintegration time of antacid tablet formulations

Antacid formulation	Neutralisation capacity (mEq acid/tablet)
"M"	23,25
"G"	21,63
"R"	13,60

TABLE 2. Neutralisation capacity values for antacid tablet formulations

	% dissolved			
	Ciprofloxacin (500 mg) without antacid	Ciproloxacin (500 mg) + M	Ciproloxacin (500 mg) + G	Ciproloxacin (500 mg) + R
Sample 1	93,61	96,44	90,68	68,68
Sample 2	94,77	96,28	87,60	78,15
Sample 3	97,21	97,34	83,76	80,52
Sample 4	98,54	95,08	86,74	75,11
Sample 5	99,86	95,91	88,66	76,59
Sample 6	97,61	96,25	89,41	79,01
$\overline{X}$	96,9320	96,2175	87,8083	76,3446
S.D.	2,3424	0,7344	2,4120	4,1996
R.S.D	2,42	0,76	2,75	5,50

TABLE 3. Amount of dissolved ciprofloxacin from tablet formulation without/with antacid addition

	% dissolved			
	Moxifloxacin (400 mg) without antacid addition	Moxifloxacin (400 mg) + M	Moxifloxacin (400 mg) + G	Moxifloxacin (400 mg) + R
Sample 1	106,10	105,04	98,98	96,30
Sample 2	103,25	102,07	100,76	94,39
Sample 3	105,21	101,97	99,85	94,34
Sample 4	102,05	105,15	101,49	94,75
Sample 5	107,71	102,13	99,69	96,49
Sample 6	101,25	103,83	102,40	95,90
$\overline{X}$	104,2620	103,3665	100,5283	95,3595
S.D.	2,4932	1,5069	1,2674	0,9808
R.S.D	2,39	1,46	1,26	1,03

TABLE 4. Amount of dissolved moxifloxacin from tablet formulation without/with antacid addition

It was demonstrated in this study, that simultaneous application of antacids ("M", "G" and "R") with fluoroquinolones (ciprofloxacin and moxifloxacin) resulted in decreased dissolution rate (in wide range of concentrations, from -0,74% to -21,24%). Neutralisation capacity of antacids does not reflect their ability to form complexes with fluoroquinolones. Antacid with highest neutralisation capacity (23,25 mEq acid/tablet) had minimal influence on dissolution rate of fluoroquinolone tablets (ciprofloxacin tablets: -0,74 %; moxifloxacin tablets: -0,86%). Disintegration time of antacid tablets has minor influence on drug quality and control. This parameter is very important in the analysis of other types of solid dosage forms. The main reason would be in the fact that antacid tablets are not swallowed, but gradually dissolved in oral cavity. Variation of disintegration time indicated the importance of this parameter, and allowed evaluation of the influence of postponed antacid-fluoroquinolone contact. In that manner, easy dissolution of tested fluoroquinolones could be established (antacid tablets with disintegration time above two hours, caused minor decrease on dissolution rate of both fluoroquinolones). Analysed antacids (two of three, "R" vs. "G"), disintegration time: "R" ≤ 40 seconds, "G" ≤ 7 minutes) with disintegration times significantly shorter than dissolution testing period (30 minutes) interacted fully with both fluoroquinolones and consequently resulted in decreased dissolution rate (ratio of relative decrease in dissolution rate with simultaneous addition of "R"/"G", was: 21,24/9,41=2,3 times for ciprofloxacin tablets and 8,54/3,58=2,4 times for moxifloxacin tablets.)

Conclusion

According to the results obtained in this study, we can conclude that dissolution rate of ciprofloxacin and moxifloxacin was downsized by simultaneous application of antacids. This influence was more pronounced in the case of ciprofloxacin, than in the case of moxifloxacin tablets.

Also, similar relationship was found in decreased dissolution rate of ciprofloxacin tablets compared to moxifloxacin (2,3 vs. 2,4) using the same antacids ("G" and " R"), under the same testing conditions. It can be assumed, that it is a consequence of similar mechanism of interaction which is not dependent of structural differences between ciprofloxacin and moxifloxacin.

Regardless of the type and neutralization capacity of analysed antacids, which posses ability to chelate fluoroquionolones, potential simultaneous application of these types of drugs (antacids and fluoroquinolones) has appreciable influence on dissolution rate of ciprofloxacin and moxifloxacin tablets.

References

(1) Oliphant C.M., Green G.M. Quinolones: a comprehensive review. Am. Fam. Physician. 2002;65(3):455-464.

(2) Luzzaro F. Fluoroquinolones and Gram-negative bacteria: antimicrobial activity and mechanisms of resistance. Infez. Med. 2008 ;16 (Suppl 2):5-11.

(3) Madurga S., Sánchez-Céspedes J., Belda I., Vila J., Giralt E. Mechanism of binding of fluoroquinolones to the quinolone resistance-determining region of DNA gyrase: towards an understanding of the molecular basis of quinolone resistance. Chembiochem. 2008; 9 (13): 2081-2086.

(4) Gilbert D.N. Urinary tract infections in patients with chronic renal insufficiency. Clin. J. Am. Soc. Nephrol. 2006;1(2):327-331.

(5) Lion C., Conroy M.C., Carpentier A.M., Lozniewski A. Antimicrobial susceptibilities of Pasteurella strains isolated from humans. Int. J. Antimicrob. Agents. 2006;27(4):290-293.

(6) Huang H.C., Shieh C.C., Yu W.L., Cheng K.C., Chen C.C., Chang S.T., Chuang Y.C. Comparing the protective effects of ciprofloxacin, moxifloxacin and levofloxacin in mice with lipopolysaccharide-induced acute lung injuries. Respirology 2008;13(1):47-52

(7) Blondeau J.M. Expanded activity and utility of the new fluoroquinolones: a review. Clin. Ther. 1999;21(1):3-40

(8) Perletti G., Wagenlehner F.M., Naber K.G., Magri V. Enhanced distribution of fourth-generation fluoroquinolones in prostatic tissue. Int. J. Antimicrob. Agents. 2008 (in press)

(9) Mittmann N., Jivarj F., Wong A., Yoon A. Oral fluoroquinolones in the treatment of pneumonia, bronchitis and sinusitis. Can. J. Infect. Dis. 2002;13(5):293-300.

(10) Dalhoff A., Shalit I. Immunomodulatory effects of quinolones. Lancet Infect. Dis. 2003; 3(6): 359-371

(11) Zhanel G.G., Fontaine S., Adam H., Schurek K., Mayer M., Noreddin A.M., Gin A.S., Rubinstein E., Hoban D.J. a review of new fluoroquinolones: focus on their use in respiratory tract infections. Treat. Respir. Med. 2006; 5(6):437-465.

(12) Pestova E., Millichap J. J., Noskin G. A., Peterson L. R. Intracellular targets of moxifloxacin: a comparison with other fluoroquinolones. J. Antimicrob. Chemother. 2000; 45: 583-590

(13) Blondeau J.M., Borsos S., Hesje C.K. Antimicrobial efficacy of gatifloxacin and moxifloxacin with and without benzalkonium chloride compared with ciprofloxacin and levofloxacin against methicillin-resistant Staphylococcus aureus. J. Chemother. 2007;19(2):146-151

(14) Ming L. J. Structure and function of "metalloantibiotics". Med Res Rev. 2003; 23(6):697-762.

(15) Žakelj S., Berginc K., Uršič D., Kristl A. Influence of metal cations on the solubility of fluoroquinolones. Pharmazie 2007;62(4):318-320.

(16) Dressman J., Krämer J. Pharmaceutical dissolution testing. Taylor &Francis, Boca Raton, London, New York, Singapore, 2005

(17) U.S. Pharmacopeia, 31st rev.; U. S. Pharmacopeial Convention, Rockville, MD, 2007

(18) European Pharmacopoeia, 6th Edition, European Directorate for the Quality of Medicines & Healthcare (EDQM), Council of Europe, Strasbourg, 2007