Physical and chemical compatibility of intravenous metronidazole infusion with physiological solutions: UV-Visible Spectroscopy study

Ali I. Al-Gareeb* Hayder M. Al-Kuraishy** Marwan S.M. Al-Nimer***

ABSTRACT

Background and Objectives: The instructions of the manufacturer showed that metronidazole infusion solution (5mg/mL) is incompatible with few drugs. This study aimed to determine the physical and chemical compatibilities of metronidazole infusion with commonly used intravenously administered physiological solutions.

Methods: Metronidazole injection in a commercially available concentration of 5mg/mL was mixed with 0.9% sodium chloride, 5% glucose saline or Ringer's solution in the infused bottle or during simulated Y-site injection. metronidazole was examined physically by visual inspection and chemically by ultraviolet-visible spectrophotometer analysis. Adsorption of metronidazole to intravenous administration sets without inline filters was also studied. Furthermore, the compatibility of metronidazole with some drugs related to beta-lactams was studied. Physical incompatibility was determined by visual inspection against a black-and-white background, and chemical incompatibility was measured by a stability-indicating UV-visible spectrophotometer assay for metronidazole.

Results: The absorbance magnitude (O.D.) recorded by UV-visible spectrophotometer showed differences in respect to the infused solutions as well as to the admixed physiological solutions. Moreover, metronidazole is incompatible with Co-amoxicillin and clavulanic acid, and cefepime.

Conclusions: It is concluded that metronidazole infusion should be separately infused, not admixed with physiological solutions and avoided its combination with beta lactams.

Key words: Metronidazole, Physiological solution, Compatibility .

INTRODUCTION:

5- nitroimidazoles included metronidazole, tinidazole, ornidazole and secnidazole are used in the treatment of anaerobic protozoan parasitic infections[1]. Metronidazole is active against a wide range of pathogenic microorganisms, notably species of bacteroides, fusobacteria, clostridia, eubacteria, anaerobic cocci, and Gardnerella vaginalis as well as protozoa. Metronidazole and metronidazole HCl are stable in air but it may darken upon exposure to light but it was degraded in solution by photolysis using ultraviolet-B light in presence of hydrogen peroxide exhibiting pseudo-first order reaction kinetics[2]. It is undergone reduction reaction, and its reduced form does not absorb at the same max of the pure metronidazole[3]. The instructions of the manufacturer showed that Metronidazole infusion solution (5mg/mL) is incompatible with cefamandole nafate, cefoxitin sodium, penicillin G potassium, dextrose 10% and sodium lactate injection. Metronidazole is incompatible with aztreonam when admixed in a phosphate citrate buffer[4] and ciprofloxacin lactate, acyclovir during simulated Y- injection under fluorescent lighting at room temperature[5,6]. In general β-lactam antibiotics containing the 2-aminothiazole moiety are incompatible with metronidazole. These antibiotics react in acidic media with the nitrite ion contributed by metronidazole producing diazotized molecule[7]. This study is aimed to show the

*Lecturer in Pharmacology Department of Pharmacology College of Medicine Al-Mustansiriya University
**Assistant lecturer in Pharmacology Department of Pharmacology College of Medicine Al-Mustansiriya University
***Department of Pharmacology College of Medicine Al-Mustansiriya University

compatibility of metronidazole in physiological solutions using UV-Visible spectroscopy determinant.

MATERIALS AND METHODS:

This study was conducted in Department of Pharmacology, College of Medicine, University of Al-Mustansiriya in Baghdad, Iraq during 2009. The pharmaceutical preparation of metronidazole intravenous infusion (500 mg/100 mL) in plastic bottle, beta lactam drugs and physiological solutions were purchased from the local sources. The ingredients of metronidazole intravenous infusion include citric acid monohydrate (22.9 mg), sodium chloride (790 mg) and anhydrous disodium hydrogen phosphate (47.6 mg), pH 5.5 (4.5-7.0). Physiological solutions included sodium chloride (0.9 % contained 150 mmol/L sodium and 150 mmol/L chloride), glucose saline (dextrose 5% w/v and sodium chloride 0.9% contained 150 mmol/L sodium, 150 mmol/L chloride, the osmolality 586 mOsm/L) and Ringer's solution (contained 147.5 mmol/L sodium, 4.0 mmol/L potassium, 156 mmol/L chloride and 2.25 mmol/L calcium, the total osmolality 310 mOsm/L). In the first series of experiments, an equal volume (100 mL) of each physiological solutions; sodium chloride , glucose saline or Ringer's was drawn and replaced with 100 mL metronidazole and let the fluid run under gravity via intravenous fluid tubing system ended with intravenous canula. Then the fluid was obtained from the bottle, at the end of tubing system and that run from canula. The visual incompatibility in term of cloud, change in color, evolution of gas and the appearance of precipitates was checked. The pH of the obtained fluid was recorded and diluted with the same physiological solution to get a final concentration of 10µg/mL and the UV-spectra of metronidazole was recorded using UV-visible spectrophotometer. In the second series of experiments, metronidazole solution was injected as pulses into canula of each running physiological solution, then the admixed solution was collected and the optic density was recorded as mentioned above. In the third series of experiments, both physiological solution and metronidazole solution were run via Y-assembly connection. The optic density was recorded as mentioned above. In the fourth series of experiments, 100 mL metronidazole (500 mg/100mL) was mixed with 400 mL of sodium chloride diluted to 1/3 and 2/3 strength or glucose saline diluted to 1/5, 2/5,3/5,4/5 strength. Then the optic density of each solution was recorded as mentioned above. In the fifth series of experiments, metronidazole solution was dissolved in 25, 50, 75 and 100 mmol potassium chloride obtaining a final concentration of 10µg/mL and the optic density was recorded as above. In the sixth series of experiments, equal volume metronidazole solution (5mg/mL) was mixed with each of beta lactam drugs; ampicillin, amoxicillin, Co-ampicillin and cloxacillin, Co-amoxicillin and clavulanic acid, cefatoxime, ceftriaxone and cefepime. The visual appearance of the mixture was observed up to 30 minutes.

RESULT:

There is no evidence of visual incompatibility and the pH was 4.9, 4.5 and 4.7 for metronidazole admixed in 0.9% sodium chloride, glucose saline and Ringer's solution respectively. Figure(1) shows that the peak absorbance (O.D.) of metronidazole admixed in the plastic bottle of sodium chloride (0.9%) solution (0.539 at λ320 nm) is higher than running plastic tube (0.316 at λ315 nm) or canula (0.286 at λ317 nm). The peak absorbance (O.D) of metronidazole admixed in plastic bottle of glucose saline solution did not differ from that admixed in the container of sodium chloride (0.9%) solution (0.539 *vs* 0.522 at at λ320 nm respectively) but the differences were observed in the running tube and canula (Figure.2). Metronidazole's peaks obtained from admixing metronidazole with Ringer's solution whether in plastic bottle, running tube or canula were differed from those observed with sodium chloride (0.9%) or glucose saline solution (Figure.3). In the

second series of experiments, the metronidazole absorbance peaks (at λ320.5-321 nm) were 0.234, 0.272 and 0.286 when metronidazole solution is injected as pulses into the canula of sodium chloride (0.9%), glucose saline and Ringer's solution infusions respectively. In the third series of experiment the highest peak of metronidazole absorbance was observed when metronidazole solution was run via Y-assembly connection with glucose saline (0.546 at λ320) compared with sodium chloride (0.456 at λ320) or Ringer's solution (0.412 at λ320.5). Table (1) shows that any change in the strength of sodium chloride (0.9%) or glucose saline solution by dilution with distilled water resulted in obvious incompatibility of metronidazole in term of changes in the magnitude of metronidazole peak. Metronidazole dissolved in different concentrations of potassium chloride solutions showed higher magnitude of absorbance peak (0.549) at λ320 nm when dissolved in 25 mmol/L and the lowest (0.524) at λ320 nm when dissolved in 50 mmol/L potassium chloride solution (Figure. 4). Table 2. shows that metronidazole is incompatible with Co-amoxicillin and clavulanate and cefepime.

Table 1: The effect of different strengths of physiological solution on the absorbance (O.D.) of metronidazole (10 µg/mL).

Physiological solution	Peak wave-length (nm)	Absorbance (O.D.)
1/3 strength sodium chloride	321.6	0.511
2/3 strength sodium chloride	319.5	0.455
Full strength sodium chloride	320.0	0.539
1/5 strength glucose saline	320.0	0.488
2/5 strength glucose saline	320.9	0.603
3/5 strength glucose saline	320.2	0.493
4/5 strength glucose saline	319.5	0.510
Full strength glucose saline	320.0	0.522

Table 2: Visual incompatibility of metronidazole admixed with some drugs related to beta latams.

Drug	Appearance of admixture	Compatibility
Ampicillin	Clear	Yes
Amocillin	Clear	Yes
Co-ampicillin and cloxacillin	Clear	Yes
Co-amoxicillin and clavulanic acid	Dark yellow color	No
Cefotaxime	Clear	Yes
Ceftriaxone	Clear	Yes
Cefepime	Precipitates	No

DISCUSSION:

There is no doubt that metronidazole showed incompatibility with physiological solutions. The causes of metronidazole incompatibility are multifactorial. The differences in UV spectra of metronidazole dissolved in different physiological solutions that obtained from plastic bottle, plastic tubing system and canula are related either to the tonisity, pH or ingredients of each physiological solution or to the adsorption of metronidazole to the plastic material. Most antibacterial agents are stable when admixed in physiological solutions e.g. doripenem[8]. Metronidazole showed incompatibility when combined with some drugs e.g. aztreonam , ciprofloxacin in 5% dextrose[9,10]. On the other hand, degradation of cefotaxime in tinidazole glucose injection is reported[11]. Although the pH of metronidazole is changed when admixed in physiological solution but it remained within the acceptance range of stability. It seems to be the buffer capacity of each physiological solution did not affect the stability of metronidazole because the pH of admixtures whether the physiological solutions with low (sodium chloride or glucose saline) or high (Ringer's solution) buffer capacity are approximated. Previous study showed that the incompatibility of metronidazole with ciprofloxacin based on pH changes of more than 1 unit [9]. The results reported herein show that the metronidazole instability is related to the some drugs related to the beta lactam as with Co-amoxicillin and clavulanic acid or cefepime or presence of potassium salts as with Ringer's solution. Compatibility of drug pairs (nitroimidazoles, macrolides and omeprazole) in their binary mixtures was found but ternary mixtures show somewhat larger interactions[12]. The possibility of adsorbing property of metronidazole on the inner surface of the plastic materials also contributed in the metronidazole instability. There is an evidence that drug incompatibility had been observed with calcium salts as with ceftriaxone with calcium chloride[13], and this evidence may explain the low value of metronidazole's absorbance when admixed in Ringer's solution. Therefore, The best way would be to inject the metronidazole separately with 100 mL prepared infusion solution to avoid the physiochemical reactions related to the preservatives and additives[14].

CONCLUSION:

It is concluded that metronidazole infusion should be separately infused, not admixed with physiological solutions and avoided its combination with beta lactams.

REFERENCES:

1. Wang FM, Qian XD, Xu H, Yu HY. Efficacy of 5-nitroimidazole derivatives in treatment of bacterial vaginosis. Zhonghua Yi Xue Za Zhi 2008; 88 (31) :2201- 3.
2. Shemer H, Kunukcu YK, Linden KG .Degradation of the pharmaceutical metronidazole via UV, Fenton and photo-Fenton processes. Chemosphere 2006 ; 63(2):269-76.
3. Deepika M, Jain A, Maheshwari RK, Patidar V. Simultaneous spectrophotometric estimation of metronidazole and norfloxacin in combined tablet formulations using hydrotrophy. Asian J Pharm 2008; 1: 357-61.
4. Bell RG, Lipford LC, Massanari MJ, Riley CM. Stability of intravenous admixtures of aztreonam and cefoxitin, gentamicin, metronisazole, or tobramycin. Am J Hosp Pharm 1986; 43 (6): 1444-53.
5. Jim LK. Physical and chemical compatibility of intravenous ciprofloxacin with other drugs.. The Annals of Pharmacotherapy 1993; 27(6): 704-7
6. Canann D, Tyler LS, Barker B, Condie C. Visual compatibility of i.v. medications routinely used in bone marrow transplant recipients. Am J Health Syst Pharm. 2009;66 (8):727-29.
7. Thakur AB, Abdelnasser M, Serajuddin AT, Wadke DA. Interaction of metronidazole with antibiotics containing the 2-aminothiazole moiety. Pharm Res 1991;8 (11):1424-29.
8. Psathas PA, Kuzmission A, Ikeda K, Yasuo S. Stability of doripenem in vitro in representative infusion solutions and infusion bags. Clin Ther 2008; 30(11):2075-87.
9. Elmore RL, Contois ME, Kelly J, Noe A, Poirier A. Stability and compatibility of admixtures of intravenous ciprofloxacin and selected drugs. Clin Ther 1996; 18(2):246-55.
10. Trissel LA, Martinez JF. Compatibility of aztreonam with selected drugs during simulated Y-site administration. Am J Health Syst Pharm 1995; 52 (10):1086-90.
11. Guo P, Li X, Wang J, You A. Study on the compatibility of cefotaxime with tinidazole in glucose

injection. J Pharm Biomed Anal 2007;43(5):1849 -1853.
12. Chadha R, Jain DV, Kumar A. Quantitative analysis of in vitro compatibility of binary and ternary mixtures of nitroimidazole and macrolides in combination with omeprazole using a calorimetric technique. Pharmazie. 2007; 62(5):327-336.
13. Nakai Y, Tokuyama E, Yoshida M, Uchida T. Incompatibility of ceftriaxone sodium with calcium -containing products. Yakugaku Zasshi. 2009;129 (11):1385-92.
14. Grenet I and Hazebroucq G. Physicochemical incompatibility of injectable drugs: practical considerations. Therapie 1995; 50(3):191-5.