In Vitro Interaction Between Zidovudine and Some Adsorptive Antacids

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ABSTRACT: The *in vitro* interaction between zidovudine and three antacids and a commercial product was investigated. The extent of adsorption of zidovudine by the antacids, and the effects of the antacids on the disintegration time and dissolution of the drug from tablets were studied. Adsorption of the drug by the antacids followed the order; magnesium trisilicate > aluminium hydroxide > magnesium hydroxide. Retardation of dissolution amongst the antacids and commercial product was of the order; Jawasil® > magnesium trisilicate > aluminium hydroxide > magnesium hydroxide. Also, the degree of retardation of dissolution from the tablets increased as the amount of adsorbent increased. Co-administration of zidovudine and adsorptive antacid formulations should be avoided in clinical practice since it can lead to a decrease in the bioavailability of zidovudine, ultimately leading to therapeutic failure.

Key words: Zidovudine, adsorption, antacids, interaction, dissolution

INTRODUCTION

A significant number of HIV-infected patients take gastric acid modifiers including antacids at different intervals during their anti-retroviral therapy.[1] A survey of 200 individuals in 2004 observed that 77 % of persons with HIV in the United States had taken antacids since initiating antiretroviral therapy, and 32 % had taken antacids within the previous month[2]. Antiretrovirals are prone to drug-drug and drug-food interactions that can result in subtherapeutic or supratherapeutic concentrations.[3]

Zidovudine, 1-(3-Azido-2,3-dideoxy-β-D-ribo-furanosyl)-5-methylpyrimidine-2,4-(1H,3H)-dione is a nucleoside reverse transcriptase inhibitor structurally related to thymidine with antiviral activity against HIV-1. It is used in the treatment of HIV infection and AIDS. The drug has been shown to decrease the rate of clinical disease progression and prolong survival in HIV infected individuals. Zidovudine undergoes a series of phosphorylation in the host cell to give zidovudine triphosphate, an antiviral triphosphate.[4,5] Zidovudine triphosphate selectively inhibits viral reverse transcriptase (RNA dependent DNA polymerase) in preference to cellular DNA polymerase.[6]

Zidovudine is rapidly absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism with a bioavailability of about 60-70%. Peak plasma concentrations occur after about 1 hour. Zidovudine crosses the blood brain barrier producing CSF to plasma ratios of about 0.5. Plasma protein binding is reported to be 34-38% with a plasma half-life of about 1 hour. It is also metabolised in the liver, mainly to the inactive glucuronide and is excreted in the urine as unchanged drug and metabolite.[7]

Drug interactions have become an increasingly complex challenge for providers treating patients with HIV infection. Despite intense research in many areas of HIV infection, there is often a lack of formal

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drug interaction studies with HIV medications making providers to often rely on their own clinical judgment and to predict drug interactions without supporting data. Zidovudine was the first antiretroviral agent to be approved and its interaction with other drugs has been well studied.[8-14] But existing data on its interactions with antacids are unavailable, hence the need to carry out this study. The aims of the study are to evaluate the effect of antacids on zidovudine absorption when administered concomitantly and to investigate the interaction and the extent of the interaction between some commonly used antacids and zidovudine.

MATERIALS AND METHODS

Zidovudine powder (Divine Essential Formulations Company Ltd., Lagos State, Nigeria), Zidovir tablets (Cipla), were gifts from the Pharmacy Department, University of Benin Teaching Hospital, Benin City, Nigeria. Magnesium trisilicate, aluminium hydroxide and magnesium hydroxide powders (BDH Poole, UK), Jawasil® Suspension (Jawa Pharmaceuticals, Lagos State, Nigeria). All other reagents were of analytical grade and were used as such.

Preparation of calibration curve of Zidovudine. Various zidovudine standard concentrations ranging from 2 - 20 µg/ml were prepared from stock solutions of 20 mg/ml drug solution in 0.1N HCl and subjected to ultra-violet spectrophotometric analysis at 266 nm (T70, PG Instruments Ltd.). Respective absorbances were taken with 0.1N HCl as blank and lines of regression were determined.

Adsorption studies. A 250 mg quantity of aluminium hydroxide was weighed into a conical flask containing 2 mg% of zidovudine solution. The resulting suspension was shaken and placed in the water bath at 37 ± 0.5°C and equilibrated for 60 min with intermittent shaking. Pre-experimentation had shown that an equilibrium state was attained after about 30 min. After equilibration, the suspension was centrifuged at 4000 rpm for 20 min. (Techmel and Techmel, Model 800, USA). After centrifugation, the drug concentration in the supernatant was determined spectrophotometrically at 266 nm against similarly prepared blank solution containing no drug. The same procedure was repeated for 0.5, 0.75, 1, 1.25, 1.5, 1.75 and 2 g quantities of the adsorbent. Similar procedures were followed for magnesium trisilicate and magnesium hydroxide. The experiments were carried out in triplicate. Adsorption isotherms were generated for the adsorbents by plotting the absorbance values obtained against concentration for each adsorbent.

Disintegration time testing. The disintegration times of zidovudine 300 mg tablets (Zidovir®) were determined in 0.1N HCl in suspensions of the adsorbents and a commercial product (Jawasil®) at 37 ± 0.5ºC using a BP disintegration test unit (Mk IV. Manesty Machines Ltd, UK). Average values were computed for 5 tablets.

Dissolution studies. The dissolution tests were carried out 900 ml of 0.1M HCl (pH 1.15) maintained at 37 ± 0.5°C. Dissolution profiles were obtained for the zidovudine tablets using a BP dissolution test apparatus (Caleva ST7, GB Caleva. UK). This was fitted with a basket rotated at 100 rpm using 900 mL of 0.1N HCl solution as dissolution medium maintained at 37 ± 0.5°C. The effect of the antacids on dissolution was studied by adding 2 g of the adsorptive antacid or 20 mL of Jawasil® to the dissolution medium. Samples were withdrawn at intervals, diluted and centrifuged at 4000 rpm for 20 min. The concentration of the drug was determined spectrophotometrically against a 0.1N HCl blank at 266 nm. Equal volumes of fresh dissolution medium were used to replace those withdrawn for analysis. The experiments were carried out in triplicate.

RESULTS

The results of the adsorption studies showed significant adsorption of zidovudine by all the adsorptive antacids. From Figures 1-3, it was observed that there was an increase in the amount of drug adsorbed as the concentration of the adsorbent increased, with magnesium trisilicate (48% of drug adsorbed by 0.02 g/ml of adsorbent) having a higher

percentage of drug adsorbed when compared to aluminium hydroxide (25% of drug adsorbed by 0.02 g/ml of adsorbent) and magnesium hydroxide (22% of drug adsorbed by 0.02 g/ml of adsorbent).

Table 1. Disintegration times of Zidovudine tablets in various media at 37 ± 0.5°C.

Disintegration medium	Antacid conc. (mg/ml)	Disintegration times (min)
0.1N HCl	0	3:40
Magnesium trisillicate (% ^{w}/v)	0.2	3:59
	0.5	4:25
	1.0	4:55
Aluminium hydroxide (% ^{w}/v)	0.2	3:50
	0.5	4:15
	1.0	4:30
Magnesium hydroxide (% ^{w}/v)	0.2	3:50
	0.5	4:10
	1.0	4:30
Jawasil®	*10 ml	4:6
	*15 ml	4:56
	*20 ml	5:30

*Each ml contains 120 mg of aluminium hydroxide, 60 mg of magnesium trisilicate and 40 mg of magnesium hydroxide.

This could be as a result of the silicate moiety present in magnesium trisilicate which is responsible for its adsorptive activity. Interaction studies between silicate and some hydrophobic molecules showed that the positive charges on the molecules promote adsorption onto silica molecules.[15] Zidovudine essentially has nitrogen atoms in its chemical structure and these provide the binding sites for the silica in magnesium trisilicate. The degree of the adsorption is also dependent on the number of free binding sites available.[16,17] In an earlier study, Dapasse postulated that the strong adsorption of some molecules onto silica is as a result of the hydrophobic properties and the positive charge of these molecules[16].

The *in vitro* adsorption studies also revealed that magnesium trisilicate had high adsorptive properties while that of magnesium hydroxide was low with aluminium hydroxide in between. The adsorption curve of magnesium trisilicate, aluminium hydroxide and magnesium hydroxide, depicts an 'L'curve which shows that the amounts of adsorbed solute increases as the equilibrium concentration increases until a plateau value is reached. This indicates that for these systems, the adsorbate molecules are likely to be adsorbed flat on the surface of the adsorbent, or vertically if there is little or no competition from the solvent for the adsorption sites.

According to the British Pharmacopoeia, an uncoated tablet disintegrates in a stipulated time of less than or equal to 15 min. Zidovir® tablets met the BP requirement in spite of delayed disintegration in the presence of the antacids (Table 1).

The effect of the adsorbents and Jawasil® on the dissolution characteristics of zidovudine tablets is illustrated in Fig. 4. The curves show that dissolution of the drug decreased in the presence of all the antacids and Jawasil®. At all the concentrations studied, the order of retardation of dissolution of zidovudine from the tablets was Jawasil® > magnesium trisilicate > aluminium hydroxide > magnesium hydroxide with 65%, 68%, 71% and 77% of the drug released in the presence of the respective antacids after 45 min. The degree of retardation of dissolution from the tablets increased as the amount of adsorbent increased (Fig. 5). Hence, after 45 min, 68% of the zidovudine was found in solution in the presence of 0.2% w/v magnesium trisilicate; 56% in the presence of 0.5% w/v magnesium trisilicate and 51% in the presence of 1% w/v magnesium trisilicate. However, in the absence of antacids from the dissolution medium the tablet formulation gave 88% dissolution in less than 45 min.

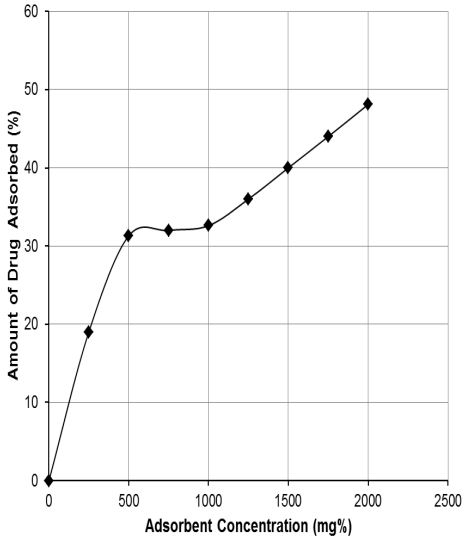

Figure 1. Adsorption of Zidovudine onto magnesium trisilicate.

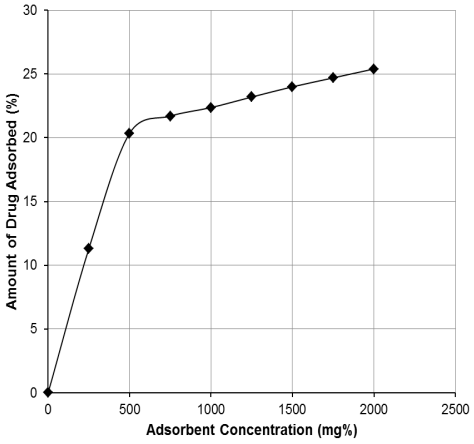

Figure 2. Adsorption of zidovudine by aluminium hydroxide.

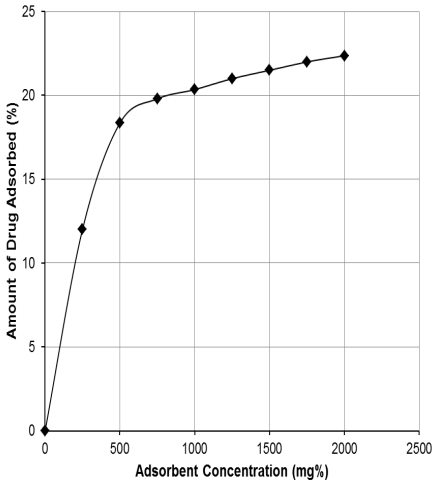

Figure 3. Adsorption of zidovudine by magnesium hydroxide.

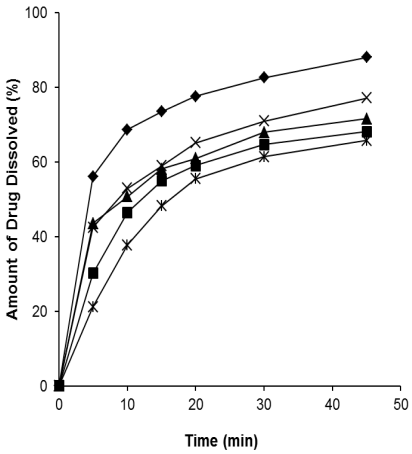

Figure 4. The dissolution of zidovudine tablets: 0.1N HCl (◆), magnesium hydroxide (×), aluminium hydroxide (▲), magnesium trisilicate (■), Jawasil (∗)

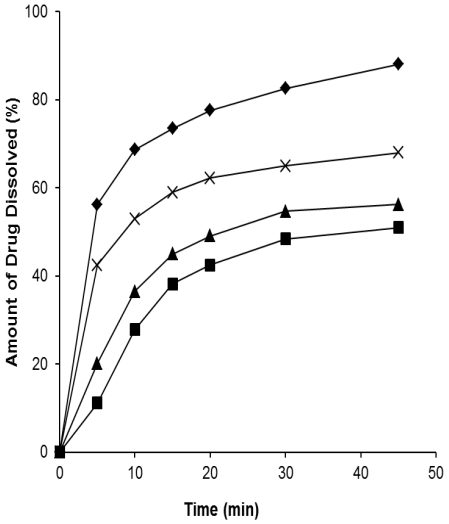

Figure 5. The dissolution of zidovudine tablets in various concentrations of magnesium trisilicate suspensions in 0.1N HCl.: 0 %^{w}/v (◆), 0.2 %^{w}/v (×), 0.5 %^{w}/v (▲), 1 %^{w}/v (■)

DISCUSSION

Adsorption is a surface phenomenon, it would be expected that the degree of adsorption will be related to particle size of the adsorbents. A larger particle surface will also be associated with increased adsorption and vice versa, although the availability of adsorption sites on the particle surface may affect the extent of adsorption.[17] In an earlier study, it was proven that aluminium hydroxide has a higher surface area than magnesium trisilicate and magnesium hydroxide[18]. It would be expected that the propensity for adsorption of solutes by the adsorbents used in this study will follow the order: aluminium hydroxide > magnesium trisilicate > magnesium hydroxide. But magnesium trisilicate deviates from this order since it has the highest adsorptive capacity for zidovudine amongst the antacids. Jawasil® ranks above all because of the combined effect of the three antacids it contains; 120 mg/ml of aluminium hydroxide, 60 mg/ml of magnesium trisilicate and 40 mg/ml of magnesium hydroxide

It may be inferred, therefore, that the apparent retardation of dissolution from the zidovudine tablets in the presence of antacids may be due to the significant interaction which occurred between the drugs that dissolved out of the tablets and the

antacids studied via relatively strong adsorptive forces. In the disintegration time determination, some antacid particles may have been attracted onto the tablet surface blocking pores through which the disintegration medium would have entered into the tablet by capillary action and thereby delaying disintegration. Blocking of the tablet pores would be expected to occur with all types of tablet irrespective of whether the tablets contain active compounds capable of interacting via adsorptive forces with adsorbents present in the disintegration medium. Such non-specific antacid-particle interaction after disintegration of the tablet would be expected to further delay dissolution.

Thus, in order to prevent therapeutic failure it is suggested that, zidovudine should not be taken concomitantly with this type of gastrointestinal medications. Alternatively, their administration should be separated by at least two to four hours to reduce the risk of interaction in the gastrointestinal tract, since this may precipitate drug adsorption by the antacids/adsorbents, and loss of systemic availability.

CONCLUSION

From this preliminary study, it can be seen that there was significant adsorption of zidovudine by the adsorptive antacids. The adsorption of zidovudine by the adsorptive antacids will reduce the amount of the active drug available for absorption. This may in turn reduce the bioavailability of the drug with subsequent drug resistance and therapeutic failure. It is therefore advisable that zidovudine should not be administered concomitantly with adsorptive antacids.

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