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# CEFUROXIME ANTACID INTERACTIONS

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**ABSTRACT**

Cefuroxime sodium a second generation semi-synthetic cephalosporin is effective for treating meningitis, lower respiratory tract infections, gonorrhea, bone and joint infections and is approved for surgical prophylaxis. There are number of synergistic and as well as antagonistic drug interactions reported for this antibiotic. Withstanding to gastric irritations caused by this antibiotic, antacids may possibly be co-administered with cefuroxime, which may result in severe adverse drug interaction.

The present work describes the effect of magnesium carbonate, magnesium hydroxide, magnesium trisilicate, megaldrate powder, sodium bicarbonate, aluminum oxide and simethicone suspension on the *in vitro* availability of cefuroxime sodium. The mechanism of interaction between antibiotic and antacids was also studied.

## INTRODUCTION

Cefuroxime sodium is a second generation semi-synthetic cephalosporin antibiotic with excellent *in vitro* activity (O'Callaghan *et al.,* 1976; Greenwood *et al.,* 1976 and Ford, 1976). It is effective for treating meningitis, lower respiratory tract infections, gonorrhea, bone and joint infections, and is approved for surgical prophylaxis (Timothy J.W. and John R.H., 1991).

There are number of drug interaction of cefuroxime reported in the literature (Griffin J.P., *et al.,* 1988; Lyon J.A., 1983; Polk R.E., 1982 and Hoignè R. *et al.,* 1980). It is physically compatible with clindamycin (Marble D.A., *et al.,* 1988), floxacillin, furosemide (Beatson C. and Taylor A., 1987) gentamicin (Janknegt R. and Neil M., 1985; Fox A.S. *et al.,* 1988), metronidazole (Janknegt R. and Neil M., 1985; Messerschmidt W., 1987 and Barnes A.R., 1990) netilmicin (Janknegt R. and Neil M., 1985) and ranitidine (Marti E. and Cervera P., 1985 and Hobbiss J.K., 1985). Cefuroxime sodium is also compatible with parenteral solutions of sodium chloride, lactated ringers, dextrose, invert sugar or sodium lactate (Timothy J.W. and John R.H., 1991). Since many drugs are weak acids or weak bases, the pH of the gastrointestinal contents may influence the extent of absorption (Daniel A.H., 1995). Cefuroxime sodium is potentially incompatible with drugs like aminoglycosides, but the compatibility depends on concentrations, specific diluents, pH and temperature (Timothy J.W. and John R.H., 1991).

It is also well established that antacids containing divalent or trivalent cations such as $Ca^{2+}$, $Mg^{2+}$ or $Al^{3+}$ depress the absorption of orally administered antibiotics (Arayne M.S., 1993; Sultana N. *et al.,* 1983; 1984) and antifungal agents like ketoconazole as they depress the acidity of the medium, required for the dissolution of later (Daniel A.H., 1995).

The present work describes the effect of magnesium carbonate, magnesium hydroxide, magnesium trisilicate, megaldrate powder, sodium bicarbonate, aluminum oxide and simethicone suspension on the *in vitro* availability of cefuroxime sodium. The mechanism of interaction between antibiotic and antacids was also studied.

## EXPERIMENTAL

***A – Material***

Cefuroxime was a gift from GlaxoWelcome Pakistan Ltd. All the antacids were of pharmaceutical grade and were used after passage through a 170 mesh screen. All chemicals used were of analytical grade.

***B – Dissolution test apparatus***

The dissolution equipment (Pharmacopoeia of US, 1980) was manufactured to the B.P. 1988 (British Pharmacopoeia 1988) standards, which included the dissolution motor and variable speed controller with a stainless steel basket assembly. The top of the basket was modified and replaced by a conical head in order to eliminate air entrapment during dissolution (Sarapu A.C. and Clark Jr. L., 1980), which is not inconsistent with the present apparatus description (US Pharmacopeial Convention, 1979). The dissolution vessel was flat bottom glass vessel with an internal diameter of 100 mm and with a capacity of 1 liter dissolution fluid. The variable speed motor was modified to reduce unwanted vibrations by the incorporation of 1000 230μF capacitor in the speed control circuit (Embil K. and Torsian G., 1979) and was maintained within ± 0.5% of the required speed.

The rotation speed of the basket assembly was fixed at 100 ± 0.5rpm throughout the experiment. The dissolution assembly was immersed in a water bath at 37 ± 0.1°C. The absorbance of cefuroxime sodium in the dissolution medium was measured on the UV/Visible spectrophotometer model Shimadzu UV 240.

***C – In vitro availability of cefuroxime sodium***

The *in vitro* availability of cefuroxime sodium reference standard was premediated in simulated gastric juice at 37°C, 48°C and 60°C on the dissolution test apparatus as described above. 0.0446 gms of cefuroxime sodium was added in 1 liter dissolution medium (0.1 M HCl or pH 4 buffer) previously maintained at the required temperature. Aliquots of 5 ml were withdrawn intermittently (at 15 minute time intervals) for 180 minutes and assayed for the drug content after appropriate dilution. The volume of dissolution fluid was maintained by adding an equivalent amount of dissolution fluid withdrawn, which had previously been maintained at the same temperature in the same bath.

***D – Interaction with Antacids***

*In vitro* interaction studies of cefuroxime sodium with various antacids were carried out 0.1M HCl and buffer of pH 4 separately. In these sets of experiments cefuroxime (0.0446 mg; 0.1 mMole) was added to the dissolution medium at zero time while 2 grams of antacid (aluminium) hydroxide, magnesium carbonate, magnesium hydroxide, magnesium trisilicate, magaldrate, simethicone and sodium bicarbonate) was added to the dissolution medium after 15 minute time interval each separately in individual experiment. Aliquots were withdrawn after every 15 minutes till three hours and assayed as before. A graph was plotted for the first order dissolution rate constant of drug concentration versus time in each set of experiment which showed drug status during and at the end of the experiments.

## RESULTS AND DISCUSSION

The results of the effect of antacid on the *in vitro* availability of cefuroxime sodium at different time intervals at pH 1 and pH 4 simulating empty and full stomach are reported in tables 1 and 2 and are plotted in figures 1 and 2. Similarly, the effect of extended temperature studies on the availability of cefuroxime at pH 1 are given in table 3. The dissolution time $T_{50}$ and $T_{90}$ of cefuroxime sodium in presence of various antacids are given in table 4.

These results clearly indicate that the *in vitro* availability of cefuroxime is depressed in presence of all antacids studied.

Eliot and Armstrong (Sultana N. *et al.,* 1983) concluded that all capsular medications were functionally inactive when given under conditions in which the contents of the stomach were neutral or alkaline. He proposed an inhibitory effect of increased pH on the dissolution of capsule itself. According to Juhl and Blaug (Sultana N. *et al.,* 1984) pH is probably not a major factor for the dissolution of capsule medications. He found that at body temperature, varying pH did not affect the average release time of the capsule, however at room temperature pH did affect the release times.

Magnesium oxide which is soluble in 0.1N hydrochloric acid exhibited an insignificant effect on the rate of dissolution of cefuroxime. After an interval of 30 minutes 81% of the drug was present in the solution which was consistant upto 60 minutes. The $T_{50}$ and $T_{90}$ values of cefuroxime in presence of magnesium oxide were found to 24.76 and 32.38 minutes respectively.

Aluminium trisilicate which is insoluble in the dissolution medium exhibited a significant retardation effect on the dissolution of cefuroxime. After an interval of 30 minutes only 57% and after 60 minutes 70% of the drug was dissolved so that $T_{50}$ and $T_{90}$ values for cefuroxime in presence of aluminium trisilicate were 26.02 and 84.92 minutes respectively.

From the results as listed in table 1 and 2, it is quite clear that the dissolution rates of cefuroxime decreased in presence of aluminium hydroxide and magnesium trisilicate (in a concentration of 0.2% W/V). Shozo *et al.* (Pharmacopoeia of US, 1980) found that magnesium trisilicate in a concentration of 2% W/V had the greatest retardation effect on the dissolution of tetracycline. After 30 minutes less than 12% tetracycline was found in solution. Similar results were obtained in our studies and presence of even lower levels of antacid (0.2% W/V magnesium trisilicate), also reduced erythromycine dissolution; the amount dissolved after 30 minutes was 13.2 and after 60 minutes 14.24% with a very high $T_{50}$ and $T_{90}$ values.

In case of aluminium hydroxide only 28.12% of the drug was present in the dissolution medium after an interval of 30 minutes and 46% of the drug was present at the end of the experiment with $T_{50}$ and $T_{90}$ values of 64.48 and 135.58 minutes respectively.

When aluminium hydroxide and magnesium trisilicate were added to the dissolution medium, they remained in suspended and undissolved state. There are two possibilities for the slow rate of dissolution, either due to increase in pH or adsorbent properties of these two antacids. From the pH studies it is quite clear that pH was not a major factor for prolonged dissolution behaviour. Chelating effect of cefuroxime with $Mg^{2+}$ and $Al^{3+}$ may be responsible for the prolonged and incomplete dissolution.

Gelusil MPS$^{R}$ tablet, a combination of aluminium hydroxide, magnesium hydroxide and dimethylpolysiloxane had the greatest retardation effect on the dissolution behaviour of cefuroxime. Only 9.04% and 13% of the drug was dissolved after 30 and 60 minutes respectively so that $T_{50}$ and $T_{90}$ for cefuroxime in presence of Gelusil MPS$^{R}$ tablets were 202.22 and 493.43 minutes.

Thus it is clear that the dissolution of cefuroxime can be retarded by small amounts of antacids containing polyvalent cations. Although it had previously been suggested that antacids decrease the dissolution of other antibiotics by raising the pH of the medium (Polk R.E., 1982 and Hoignè R. *et al.,* 1980) and the dissolution rate is markedly reduced at high pH values (British

Pharmacopoeia, 1988), there was no significant increase in pH by the addition of these antacids in the dissolution medium. Table 5 shows the pH of the antacids in distilled water and in 0.1N HCl.

On the other hand cefuroxime was found to be strongly adsorbed on various antacids. Figure 2 shows the data ploted according to the langmuir equation (Sarapu A.C. and Clark Jr. L. 1980), which may be written as:

$$\frac{c}{x/m} = \frac{1}{ab} + \frac{c}{b}$$

where $c$ is equilibrium concentration of the solute, $x/m$ is the amount of solute adsorbed per unit weight of the adsorbent, and $a$ and $b$ are constants. The adsorption capacities of the antacids are also listed in table 3. Magnesium trisilicate and Gelusi MPS$^R$ exhibited relatively higher adsorption capacities.

Table 1
*In vitro* availability of cefuroxime sodium in presence of antacids at pH 1

| Time (min) | Cefuro xime | Cefuroxime (Moles x$10^{-5}$) in presence of | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $Mg(OH)_2$ | $MgCO_3$ | Trs | $Al(OH)_3$ | $NaHCO_3$ | Mgld | Smth |
| 0 | 1.181 | 1.168 | 1.416 | 1.230 | 1.082 | 1.471 | 1.880 | 1.051 |
| 15 | 2.127 | 1.564 | 1.700 | 1.970 | 1.686 | 1.799 | 1.898 | 1.156 |
| 30 | 3.093 | 1.743 | 2.016 | 2.189 | 1.929 | 1.873 | 2.065 | 1.261 |
| 45 | 4.050 | 1.824 | 2.139 | 2.319 | 2.059 | 1.935 | 2.251 | 1.302 |
| 60 | 5.077 | 1.891 | 2.143 | 2.473 | 2.139 | 1.996 | 2.306 | 1.342 |
| 75 | 6.004 | 1.966 | 1.978 | 2.541 | 2.183 | 2.096 | 2.337 | 1.397 |
| 90 | 6.920 | 2.016 | 1.978 | 2.609 | 2.238 | 2.152 | 2.368 | 1.412 |
| 105 | 7.841 | 2.073 | 1.991 | 2.659 | 2.263 | 2.197 | 2.395 | 1.459 |
| 120 | 8.794 | 2.120 | 2.047 | 2.622 | 2.299 | 2.242 | 2.414 | 1.502 |
| 135 | 9.565 | 2.142 | 2.090 | 2.603 | 2.350 | 2.287 | 2.410 | 1.552 |
| 150 | 10.00 | 2.159 | 2.077 | 2.591 | 2.376 | 2.325 | 2.405 | 1.620 |
| 165 | 10.00 | 2.176 | 2.089 | 2.634 | 2.393 | 2.325 | 2.393 | 1.638 |
| 180 | 10.00 | 2.193 | 2.102 | 2.820 | 2.362 | 2.319 | 2.380 | 1.682 |

It is thus clear that the dissolution of cefuroxime can be retarded by antacids containing polyvalent cations. These studies indicated that cefuroxime is strongly adsorbed on antacids, magnesium trisilicate and gelusil tablets (powdered) exhibited relatively higher adsorption capacities. The difference in the adsorption capacities could not be related to the pH of the antacids suspensions. The adsorption of cefuroxime by antacids may be responsible for the marked retardation of dissolution and hence the absorption of cefuroxime. A similar mechanism was reported for the inhibited dissolution of glycosides (US Pharmacopeial Convention, 1979), contraceptive steroids (Embil K. and Torsian G. 1979) and tetracyclines (Polk R.E., 1982 and Hoignè R. *et al.*, 1980).

Table 2
*In vitro* availability of cefuroxime sodium in presence of antacids at pH 4

| Time (min) | Cefuro-xime | Cefuroxime (Moles x$10^{-5}$) in presence of | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $Mg(OH)_2$ | $MgCO_3$ | Trs | $Al(OH)_3$ | $NaHCO_3$ | Mgld | Smth |
| 0 | 1.181 | 2.510 | 2.028 | 2.430 | 2.127 | 2.158 | 2.158 | 2.077 |
| 15 | 2.127 | 2.640 | 5.862 | 5.361 | 3.648 | 4.572 | 4.572 | 2.090 |
| 30 | 3.092 | 2.572 | 6.072 | 5.602 | 3.854 | 4.990 | 4.990 | 2.288 |
| 45 | 4.050 | 2.507 | 6.227 | 5.701 | 4.060 | 5.034 | 5.034 | 2.461 |
| 60 | 5.077 | 2.442 | 6.221 | 5.691 | 4.266 | 4.984 | 4.984 | 2.577 |
| 75 | 6.004 | 2.399 | 6.286 | 5.701 | 4.471 | 5.031 | 5.036 | 2.696 |
| 90 | 6.920 | 2.350 | 6.351 | 5.683 | 4.625 | 5.077 | 5.077 | 2.733 |
| 105 | 7.841 | 2.325 | 6.561 | 5.594 | 4.706 | 5.083 | 5.083 | 2.769 |
| 120 | 8.794 | 2.295 | 6.476 | 5.505 | 4.699 | 5.027 | 5.027 | 2.789 |
| 135 | 9.565 | 2.269 | 6.287 | 5.417 | 4.693 | 4.922 | 4.922 | 2.795 |
| 150 | 10.00 | 2.253 | 6.100 | 5.306 | 4.687 | 4.888 | 4.883 | 2.795 |
| 165 | 10.00 | 2.238 | 5.967 | 5.192 | 4.681 | 4.854 | 4.854 | 2.782 |
| 180 | 10.00 | 2.220 | 6.023 | 5.040 | 4.645 | 4.787 | 4.687 | 2.770 |

Table 3
Effect of temperature on the *in vitro* availability of cefuroxime at pH 1

| S.No | Time (min) | Drug concentration (Moles x$10^{-5}$) at | | |
|---|---|---|---|---|
| | | 37°C | 48°C | 60°C |
| 1 | 0 | 5.256 | 5.194 | 8.53 |
| 2 | 15 | 1.181 | 1.416 | 1.620 |
| 3 | 30 | 1.527 | 1.669 | 1.923 |
| 4 | 45 | 1.682 | 1.793 | 2.009 |
| 5 | 60 | 1.836 | 1.948 | 2.096 |
| 6 | 75 | 1.941 | 2.053 | 2.195 |
| 7 | 90 | 2.034 | 2.213 | 2.312 |
| 8 | 105 | 2.077 | 2.232 | 2.121 |
| 9 | 120 | 2.121 | 2.337 | 1.972 |
| 10 | 135 | 2.170 | 2.325 | 1.966 |
| 11 | 150 | 2.189 | 2.343 | 1.880 |
| 12 | 165 | 2.195 | 2.381 | 1.880 |
| 13 | 180 | 2.195 | 2.393 | 1.508 |

A number of mechanisms have been reported in the literature based on the changes in the pH of gastric fluid leading to degradation or depressed dissolution and absorption of the antibiotic.

Chelation is also considered to be the mechanism responsible for the decreased absorption of the antibiotic in the presence of antacids (Hanstein P.D., 1979).

Table 4
Dissolution of cefuroxime in presence of various antacids

| Sample | $T_{50\%}$ | $T_{90\%}$ | K |
|---|---|---|---|
| Cefuroxime | 67.79 | 122.03 | $4.02 \times 10^{-2}$ |
| Cefuroxime + Magnesium hydroxide | 379.13 | 682.44 | $1.49 \times 10^{-3}$ |
| Cefuroxime + Magnesium carbonate | 361.09 | 649.97 | $1.55 \times 10^{-3}$ |
| Cefuroxime + Magnesium trisilicate | 172.47 | 310.46 | $3.36 \times 10^{-3}$ |
| Cefuroxime + Aluminium hydroxide | 381.03 | 685.85 | $1.50 \times 10^{-3}$ |
| Cefuroxime + Sodium bicarbonate | 354.83 | 638.70 | $1.60 \times 10^{-3}$ |
| Cefuroxime + Megaldrate | 378.15 | 680.67 | $1.51 \times 10^{-3}$ |
| Cefuroxime + Simethicone | 535.07 | 963.13 | $1.02 \times 10^{-3}$ |

Table 5
Adsorption capacities towards cefuroxime and pH behaviour of antacids
in water and in 0.1N HCl

| Antacid | pH in* | | Adsorption capacity** [mg (mmoles) / gm] for cefuroxime |
|---|---|---|---|
| | $H_2O$ | HCl (0.1 N) | |
| Magnesium hydroxide | 10.70 | 1.85 | 100 (0.136) |
| Magnesium carbonate | 9.7 | 1.6 | 153 (0.208) |
| Magnesium tricilicate | 9.60 | 1.37 | 429 (0.584) |
| Aluminium hydroxide | 7.60 | 1.25 | 270 (0.367) |
| Sodium bicarbonate | 8.73 | 1.33 | 15 (0.02) |
| Megaldrate | 7.92 | 1.29 | 252 (0.351) |
| Simethicone | 1.5 | 1.2 | 438 (0.596) |

pH of distilled water = 7.00
pH of 0.1N HCl = 1.10
* = antacid concentration 0.2% W/V
** = antacid concentration 1% W/V

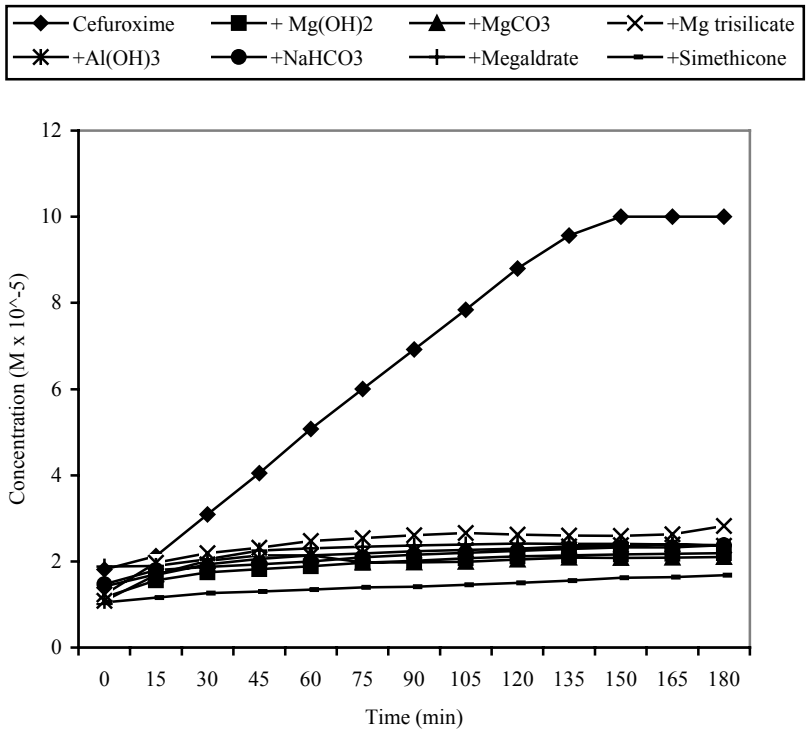


Fig. 1: *In vitro* availability of cefuroxime in presence of antacids at pH 1.

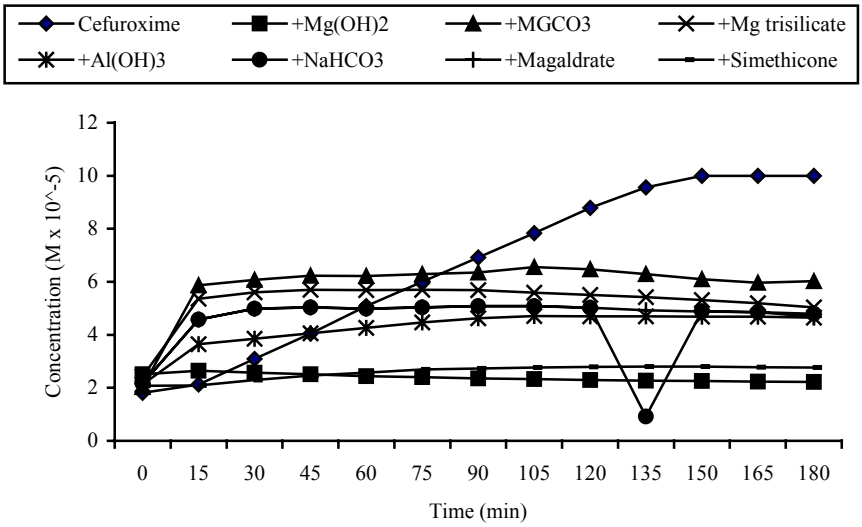


Fig. 2: *In vitro* availability of cefuroxime sodium in presence of antacids at pH 4.

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