Review Article

Consequences of Drug Interactions: A Concised Review

Lakshmi Prasanna Jakka*, Vallampati Prudhvi, Geetha Rani Valaparla, AMS Sudhakar Babu
A. M. Reddy Memorial College of Pharmacy, Petlurivaripalem, Narasaraopet, India.

ARTICLE INFO

Received: 30 Jan 2018
Accepted: 23 Feb 2018

ABSTRACT

Drug-drug interactions arise when the effects of one drug are altered by the coadministration of another. Interactions are classified as pharmacokinetics-related, where drug absorption, distribution, metabolism or excretion is affected, or pharmacodynamics-related, when drugs with similar pharmacological actions are co-prescribed. In pharmacodynamic interactions, synergism effect causes increased drug efficacy; it causes toxic effects to the body, antagonism effect causes therapeutic failure of the drug. These can be complex and time dependent nature. A sound knowledge on drug interaction and their mechanism is required for optimal therapy. In drug interactions, enzymes also play a key role in drug interactions. Either by induction and inhibiting mechanisms. Mechanisms involved in enzyme induction may be increased enzyme synthesis, decreased rate of enzyme degradation, enzyme stabilisation or enzyme inactivation. Mechanism involved in inhibition decreased drug metabolising ability of an enzyme. The present review mainly focuses on the way in which the pharmacokinetics and pharmacodynamics gets altered in various conditions and mechanisms involved in drug interaction.

Keywords: Drug-Drug interactions, Enzyme induction, Enzyme inhibition, Pharmacodynamics, Pharmacokinetics.

1. INTRODUCTION

Drug interactions are said to occur when the pharmacological activity of drug is altered by the concomitant use of another drug or by the presence of food, drink or environmental chemicals. The drug whose activity is affected by such an interaction is called object drug. The agent which precipitates such an interaction is referred to as the precipitant drug. Interactions are generally quantitative where the intensity of effect is changed can increase or decrease and seldom quantitative. An enhanced...
Pharmacological activity can be seen in Haemorrhagic tendency of warfarin when phenylbutazone is given subsequently. Decreased therapeutic activity is observed with loss of efficacy resulted due to decrease in therapeutic activity of tetracycline when concomitantly administered with food, antacids or mineral supplements containing heavy metal ions.

2. MECHANISMS OF DRUG INTERACTIONS
The three major mechanisms can cause an interaction to develop are:
1. Pharmacokinetic interactions.
2. Pharmacodynamic interactions.

Pharmacodynamic Interactions:
Pharmacodynamic interactions are those in which the activity of the object drug at its site of action is altered by the precipitant. These interactions may be direct & indirect.

Direct Pharmacodynamics Interactions:
It is one in which drugs having similar or opposing pharmacologic effects are used concurrently. The following are the three consequences of direct interactions.

Antagonism:
The condition of the interacting drugs having opposing actions is called Antagonism. This can be seen Acetylcholine with Noradrenaline have opposite effects on Heart rate. Another example is Antiparkinson drug Levodopa action can be antagonised by dopamine antagonist, haloperidol & chlorpropamide.

Additive effect (or) Summation:
The condition in which the interacting drugs have similar actions and resultant effect is the sum of individual drug responses is called Additive effect. This is happens Hydrocortisone with Hydrochlorothiazide together can produce additive side effects of hyperglycaemia or hypokalaemia. Another example co administration of salicylates & anticoagulants result in the increased risk of bleeding.

Synergism:
The condition of enhancement of action of one drug by another drug. This can be seen Alcohol enhances the analgesic effect of aspirin. Another example oestrogen with Warfarin leads to increased anticoagulation.

Indirect Pharmacodynamic Inactions:
Indirect Pharmacodynamic in both the object and the precipitant drugs have unrelated effects but the precipitant. Drug in some way alters the effects of the object drug. This effect can be seen in salicylates decrease the ability of platelets to aggregate thus impairing the haemostasis of warfarin induced bleeding occurs. The resultant effect of all pharmacodynamic interactions is thus altered with drug action change in plasma concentration.

Pharmaceutical Interactions:
It is a physicochemical interaction that occurs. When drugs are mixed in intravenous infusion causing precipitation or inactivation of the active principle such interaction are expressed by the term compatibility.

Ex: Ampicillin with dextran in solutions and are broken down (or) form chemical complexes.

Pharmacokinetic Interactions:
These are those in which the absorption; distribution; metabolism and or excretion (i.e...ADME) of the object drug are altered by the precipitant. The resultant effect is altered plasma concentration of the object drug. These are most common and often result in differences in pharmacologic effects. Clinically; important effects are precipitated by drug having low therapeutic indices (digoxin).

Interactions affecting absorption of drugs:
Drug distributions can affect drug absorption by effecting the dissolution of the drug in the stomach by influencing gastric emptying or intestinal blood flow or by inhibition of active transport processes. Certain drug combinations can affect the rate or extent of absorption of anti-infective by interfering with one or more of these mechanisms.

Generally a change in the extent of a medication’s absorption of greater than 20% may be considered clinically significant. Drug dissolution in the stomach can be modulated by gastric ph. changes or by complexation or chelation of drug.

Change in pH:
The degree of absorption ionisable drug from the stomach or duodenum depends on the pKa of the drug and the pH of the environment. In general alkalization agents such as bicarbonate salts decreases the absorption of weak acids (NSAIDS, Vitamin antagonists); having a pKa between approximately 2.5 and 7.5. Acidifying agents such as citric and tartaric acids affects the absorption of weak bases having a pKa between approximately 5 & 11 (prooxyphene & reserpine).

Effects of Gastric Emptying:-
Gastric emptying controls the length of time that a drug remains in the stomach. The longer a drug remains in the stomach; the slower it is absorbed increasing the rate of gastric emptying increases the rate of drug absorption.

Effects of Intestinal Blood Flow:-
Intestinal blood flow can be the rate limiting step in the absorption of some lipophilic drug.

Ex: intestinal blood flow can be modulated by vasodilation and vasoconstrictors and hypothetically affect the absorption of lipophilic drugs.

Complexation and Chelation:
Some drugs can interact to form complexes that are poorly absorbed. all these examples of drug interactions affecting absorption tabulated below.

Table 1: Influence of drug interactions on Absorption of Drugs

<table>
<thead>
<tr>
<th>Condition affecting absorption of Object drug</th>
<th>Precipitant drug</th>
<th>Influence on Object drug</th>
</tr>
</thead>
</table>

© International Journal of Pharma Research and Health Sciences. All rights reserved
Competitive Displacement which results when two drugs are capable of binding to the same site on the protein and when the displace drug has a higher degree of affinity than the drug to be displaced. In such situations; displacement of even a small % of drug results in a tremendous increase in the free form of the drug which precipitates increased. Therapeutic of toxic effects.

Interactions affecting distribution of drugs:
Drug distribution also gets affected by the drug interactions which results due to competition between drugs for binding to proteins, tissues and displacement of the drug by another drug. Competitive Displacement which results when two drugs are capable of binding to the same site on the protein causes the most significant interactions. Greater risk of interactions exist when the displace drug is highly protein bound (>95%) has a small volume of distribution and has narrow therapeutic index (warfarin) and when the displacer drug has a higher degree of affinity than the drug to be displaced. In such situations; displacement of even a small % of drug results in a tremendous increase in the free form of the drug which precipitates increased. Therapeutic of toxic effects.

Table 2: Influence of drug interactions on Distribution of drugs

<table>
<thead>
<tr>
<th>Object drug</th>
<th>Precipitant drug</th>
<th>Influence on Object drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulants,salicylates</td>
<td>Increased clotting time and increased risk of haemorrhage by the displacement of warfarin from its protein binding site.</td>
<td></td>
</tr>
<tr>
<td>Methotrexate, salicylic acid</td>
<td>Increased methotrexate toxicity.</td>
<td></td>
</tr>
<tr>
<td>Phenytion, valproic acid</td>
<td>Phenytion toxicity.</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea’s Insulin (tolbutamide)</td>
<td>Exerts therapeutic effects by displacing insulin from protein binding sites in pancreas; plasma and other regions resulting in its elevated levels.</td>
<td></td>
</tr>
</tbody>
</table>

3. INTERACTIONS AFFECTING DURING METABOLISM OF DRUGS

Drug-drug interactions involving metabolism are one of the principle problems in clinical practise to evaluate the pharmacological adverse effects of drugs. The most important and most common cause of pharmacokinetic interactions is alteration in the rate of bio-transformation of drugs. Major problems arise when one drug either induces or inhibits the metabolism of another drug. The enzymes mainly involved in interactions due to metabolism or the human liver microsomal P450 enzymes.

Induction:
The phenomenon of increased drug metabolising ability of the enzymes by several drugs and chemicals is called as enzyme induction. The agents which bring about such an effect are known as inducers. Most inducers are in general lipophilic compounds with long elimination half-life. Mechanisms involved in enzyme induction may be increased enzyme synthesis, decreased rate of enzyme degradation, enzyme stabilisation or enzyme Inactivation.

Enzyme induction generally results two major consequences: Increased metabolic clearance which results in reduced pharmacological activity or therapeutic efficacy. Activation of inactive or prodrug into an active metabolic which results in increase in concentration of active metabolite that leads to increased toxicity.

Table 3: Interaction involving enzymatic induction

<table>
<thead>
<tr>
<th>Object drug</th>
<th>Precipitant drug</th>
<th>Influence on Object drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Caffeine, Clozapine, R-warfarin , Tacrine, theophylline</td>
<td></td>
</tr>
<tr>
<td>CYP2C9/10</td>
<td>Phenytion, S-warfarin , tolbutamide</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Amtriptyline, clomipramine, Diazepam, Imipramine, Omeprazole, Phenytion, Propranolol</td>
<td></td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chlorozaxone, halothane, methoxyflurane</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Amiodarone, Amtriptyline, clomipramine, Codeine, desipramine, dextromethorphan , encaimide/flecainide, fluvoxamine, imipramine, metoprolol, mexiletine, nortriptyline ,Perphenazine, propafenone, propranolol, thoridazine, Timolol</td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Inducers of CYP Enzymes

| All | Phenobarbital, phenytion |
| CYP2E1 | Isoniazid |
| CYP3A1 | Spironolactone |
| CYP3A4 | Carbamazepine, rifampin |
Inhibition:

A decreased in the drug metabolising ability of an enzyme is called as enzyme inhibition. The process of inhibition is of three types.

1. Competitive
2. Non-competitive
3. Un-competitive

Inhibition Mechanism of Drug Metabolism P450:

Drug metabolism by P450 can be inhibited by three mechanisms. The first is mutual competitive inhibition caused by co-administration of drug metabolised by the same P450 isozyme.

Table 5: Interaction involving enzymatic inhibition

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>CYP1A2</th>
<th>CYP2C9/10</th>
<th>CYP2C19</th>
<th>CYP2D6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine, grapefruit juice, Cimetidine</td>
<td>Fluvoxamine, omeprazole</td>
<td>Fluoxetine, fluvoxamine, enoxacin</td>
<td>Fluoxetine, haloperidol, Paroxetine, quinidine, Cimetidine, Flucloxacillin, clindamycin, diltiazem</td>
<td>Cimetidine, Fluoxetine, haloperidol, Paroxetine, quinidine, Cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, miconazole, Ritonavir</td>
<td></td>
</tr>
</tbody>
</table>

1) Competition Inhibition:

It is a pattern of the inhibition where the inhibitor competes with the drug for same binding site within an enzyme protein. This competitive inhibition can be overcome by raising sufficiently increasing the concentration of substrate.

It is most common type of inhibition.

$\text{E+S } \leftrightarrow \text{ ES } \rightarrow \text{ E+P}$

Rate of metabolism = $\frac{V_{\text{max}}}{[\text{S}]+K_m}$

$V_{\text{max}} = \text{ maximum metabolic rate.}$

$\text{I} = \text{ Inhibiting agent concentration.}$

$\text{S} = \text{ Substrate concentration.}$

In theophylline develop nausea and when enoxacin is added to theophylline.

The nausea is associated with an elevated concentration of theophylline caused by inhibiting the metabolism of theophylline.

The increased theophylline concentration in plasma return to pre-enoxacin value when enoxacin is withdrawn.

Provided that the inhibition constant.

One pharmacokinetic defines the average concentration of drug at plateau.

\[ c_{s\text{ss,avg}} = \frac{f \times 	ext{dose}}{c_{\text{cl}} \times x} \]

The other equation defines the new (longer) half-life of theophylline ($t_{1/2\text{inhibited}}$) in relation to the normal half-life ($t_{1/2\text{normal}}$)

\[ t_{1/2\text{inhibited}} = \frac{c_{\text{normal}}}{c_{\text{inhibited}}} \frac{t_{1/2\text{normal}}}{c_{\text{inhibited}}} \]

Where $c_{\text{normal}}$ and $c_{\text{inhibited}}$ are the clearances of theophylline in the absence and presence of inhibitor; respectively.

Enoxacin does not affect the volume of distribution of theophylline.

The half-life of theophylline in absence of enoxacin is 8.8hrs & as expected with such a short half-life the plateau concentration ($C_{\text{avg,ss}}$) is approximately 4mg/L is reached within 2days of starting the theophylline regimen.

When enoxacin added to the theophylline regimen the plasma concentration rises to a new plateau; approximately 9mg/L determined by the new; and lower; clearance value (Cl $\text{inhibition}$) according to.

\[ \text{Cl}_{\text{inhibition}} = \frac{f \times \text{dose}}{c \times k \times x} \]

Graded effect:

The graded nature of inhibition of metabolism that for each metabolic pathway operating according to michaelis-menton constant type kinetics.

Rate of metabolite formation = $V_{\text{max}}/K_m \times c$

C is the concentration of the unbound drug at the enzymes site. In terms of intrinsic clearance associated with metabolite formation; $\text{Cl}_{\text{int}}$:

$\text{Cl}_{\text{int}} = f \times \text{Cl}_{\text{norm}} \times \text{Cl}_{\text{inhibited}}$

Where; fm is the fraction of the drug that is converted to a metabolite.

\[ \text{Cl}_{\text{norm}} = \frac{f \times \text{Cl}_{\text{int}}}{\text{Cl}_{\text{inhibited}}} \]

Where $C_1$ is the unbound concentration of the inhibitor $K_i$ is the inhibition constant.

Lower the $k_c$ the more potent is the inhibitor.

The longer the half-life of an inhibitor; the more persistent is inhibition of withdrawing it.

The inhibition of theophylline by enoxacin is not an all- or none effect; but rather; with all interactions a graded one.
The degree of inhibition varies with the plasma concentration.

Two conclusions can be drawn from the rate of metabolism:
1) The degree of inhibition of a particular pathway depends on the unbound inhibitor concentration relative to its $k_i$.
2) The impact of inhibition of drug elimination depends on $f_m$ and whether response lies with drug or metabolite formed.

\[
cl_{inhibited} = cl_{normal} \left[ \frac{fm}{1 + k_{intact} \cdot \frac{cu}{k_1 \cdot k_2}} + (1 - fm) \right]
\]

$K_{intact}$ = Rate constant that relates the maximum rate of inactivation of the enzyme by the inhibitor to the amount of active enzyme remaining.

$k_E$ = Endogenous degradation rate constant.

**Uncompetitive Inhibition:**

It is a pattern of inhibition where the inhibitor binds only to the enzyme forming a complex with the drug.

\[
E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \rightarrow E + P
\]

$ES + I \rightleftharpoons EIS$

Unlike competitive and non-competitive inhibition the inhibitor cannot binds to the free enzyme.

The metabolic rate can be expressed by the following equation.

\[
V = \frac{V_{\text{max}}}{1 + \frac{k_m}{k}}
\]

The inhibition becomes more market with increasing substrate concentration.

The degree of inhibition depends on the inhibition pattern when substrate concentration is high.

But when the substrate concentration is much lower than $k_m$ ($k_m >> s$) the degree of inhibition (R) is expressed by following equation.

\[
R = \frac{V(\text{+INHIBITOR})}{V(-\text{INHIBITOR})} = \frac{1}{1 + \frac{I}{K_I}}
\]

In clinical situations the substrate concentration is usually much lower than $k_m$.

**Table 6: Examples For Enzyme Inhibition**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid with Phenyoit</td>
<td>Increased absorption of folic acid due to its efficient absorption.</td>
</tr>
<tr>
<td>Coumarins with Metronidazole</td>
<td>Increased anticoaagulant activity.</td>
</tr>
<tr>
<td>Oral hypoglycaemic</td>
<td>with hypoglycaemia be precipitated.</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td></td>
</tr>
</tbody>
</table>

**Non-Competitive Inhibition:**

Clearance of the substrate in presence and absence of the inhibitor.

\[
cl_{inhibited} = cl_{normal} \left[ \frac{fm}{1 + k_{intact} \cdot \frac{cu}{k_1 \cdot k_2}} + (1 - fm) \right]
\]

If $f_m$ is the fraction of drug normally eliminated by the affected pathway; then.

\[
cl_{inhibited} = cl_{normal} \left[ \frac{fm}{1 + k_{intact} \cdot \frac{cu}{k_1 \cdot k_2}} + (1 - fm) \right]
\]
Interactions with alcohol:
The effects of interactions between alcohol and different drugs depend on whether the consumption of alcohol is chronic (or) acute.

Table 7: Effect Of Alcohol Consumption On Various Drugs

<table>
<thead>
<tr>
<th>WITH CHRONIC ALCOHOLABUSE:</th>
<th>Decreased sedative effect of barbiturates</th>
</tr>
</thead>
<tbody>
<tr>
<td>The effect of anticoagulants due to increased barbiturate metabolism may be dramatically decreased because of the increased rate of their biotransformation due to behaviour of alcohol as an enzyme inducer.</td>
<td></td>
</tr>
</tbody>
</table>

| WITH ACUTE ALCOHOL ANTI COAGULANTS: | Increased anticoagulant effects of both oral anti coagulants and heparin have been reported because of decreased metabolism due to the behaviour of alcohol as an enzyme inhibitor. |
| INGESTION: | |
| CYCLOSPORIN: | Increasing the toxicity of cyclosporin occurs. |
| FELODIPINE: | Calving ADRS. Ex: Orthostatic Hypotension. |
| ISONIAZID: | Increased incidence of hepatitis. |
| METHOTREXATE: | Cause hepatotoxicity. |
| ASPRIN: | Cause bleeding. |
| PHENOTHIAZINES: | Caused impaired motor coordination. |
| PHENYL BUTAZON E: | |

Influence of Tobacco Smoke:
Tobacco smoke is considered a self-inflicted effectors of drug metabolism. Inhalation of tobacco smoke with its more than 3000 chemical components may be considered a different way of ingesting pyrolysis products. It affects drug therapy by both pharmacokinetic and pharmacodynamic mechanisms.

Pharmacokinetic drug interactions involving the following drugs:
Pharmacokinetic interactions may call for larger doses of certain drugs due to increased in plasma clearance. Decrease in absorption, An induction of main drug &Metabolising enzyme systems.
Examples of pharmacokinetic drug interactions:
Theophylline, Tacrine, Insulin, Imipramine, Haloperidol, Pentazocine, Flecainide, Estradiol, Propranolol,Diazepam, Chlordiazepoxide.

Pharmacodynamic drug interactions involving the following drugs:
Pharmacodynamic interactions may increase the risk of adverse events in smokers with certain pathologies such as cardiovascular (or) PUD:
However, the most common effect of tobacco smoke is assumed to be an increase in drug biotransformation through induction of specific enzyme activities.
Measurements of plasma levels of certain drugs due to increased metabolism either by the intestinal mucosa (or) first-pass through the liver.
Examples of pharmacodynamic drug interactions:
Anti-hypertensive drugs, Anti angina drugs, Anti lipidemics, Oral contraceptives, Histamine-2-receptor antagonists.

Table 8: Effect Of Tobacco Consumption On Various Drugs

| WITH ANTI PSYCHOTICS +BENZODIAZEPINES: | Decreased CNS depressant in case of concurrent consumption with benzodiazepines |
| ANTI DEPRESSANTS: | |
| CYCLOSPORIN: | Increasing the toxicity of cyclosporin occurs. |
| FELODIPINE: | Calving ADRS. Ex: Orthostatic Hypotension. |
| ISONIAZID: | Increased incidence of hepatitis. |
| METHOTREXATE: | Cause hepatotoxicity. |
| ASPRIN: | Cause bleeding. |
| PHENOTHIAZINES: | Caused impaired motor coordination. |
| PHENYL BUTAZON E: | |

Drug Interactions Effecting Excretion Of Drugs:-
The renal excretion of drugs (or their metabolites) may be affected by a co-administered drug in various ways. A change in a glomerular filtration rate; tubular secretion or urinary pH can alter the elimination of some drugs.

4. CONCLUSION
Drug interactions have major role in Therapeutic management of disease, it may produce beneficial or adverse effects based on the type of interactions. Much attention needs to be paid before going to prescribe or taking medication. Enzymatic inhibition & induction also play a role in Drug interaction as they a clinically relevant effect in presence of drugs with a low therapeutic index, a long half-life and a higher bound with plasma proteins.

5. ACKNOWLEDGEMENTS
The authors are thankful to A.M. Reddy Memorial College for providing facilities for bringing out this work.
## Table 9: Interactions affecting excretion of drugs

<table>
<thead>
<tr>
<th>Interactions affecting excretion of drugs</th>
<th>OBJECT DRUG(S)</th>
<th>PRECIPITANT DRUG(S)</th>
<th>INFLUENCE ON OBJECT DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in active tubular secretion</td>
<td>Pencillin, PAS, cephalosporin, nalidixic acid, dapsone, methotrexate</td>
<td>Probenecid</td>
<td>Elevated plasma levels of acidic drugs: risk of toxic reactions.</td>
</tr>
<tr>
<td></td>
<td>Procainamide</td>
<td>Cimetidine</td>
<td>Increased plasma levels of basic object drugs: risk of toxicity.</td>
</tr>
<tr>
<td></td>
<td>Acetohexamide</td>
<td>Phenylbutazone</td>
<td>Increased hypoglycemic effect.</td>
</tr>
<tr>
<td></td>
<td>Amphetamine, tetracycline, Antacids, thiazides, acetohexamide, Quinidine</td>
<td>Antacids, thiazides, acetohexamide</td>
<td>Increased passive reabsorption of basic drug, increased toxicity.</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>Salicylates, NSAIDS</td>
<td>Reduction of renal clearance.</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>Amiodarone, quinidine, verapamil, spironolactone</td>
<td>Digoxin excretion can be reduced this will increases its toxicity.</td>
</tr>
<tr>
<td>Changes in renal blood flow</td>
<td>Lidocaine</td>
<td>Propranolol</td>
<td>The lower hepatic clearance of lidocaine when given together with propranolol. Propranolol diminishes cardiac output and hence hepatic blood flow; which in turn; reduces the clearance of lidocaine a drug highly extracted by the liver presumably because the degree of adrenergic blockade is a graded response; the interaction with lidocaine is independent on the plasma concentration of propranolol. Imipenem (antibiotic), Imipenem is extensively metabolised in kidney by a dehydropeptidase; located at the brush border of the proximal tubular cell, consequently the urinary excretion of extent imipenem is low and often insufficient to guarantee effective treatment of urinary tract infections. To improve the efficacy of imipenem it is marketed in the combination with cilastatin; dehydropeptidase inhibitor; which markedly increases the urinary excretion of unchanged imipenem.</td>
</tr>
<tr>
<td>Altered clearance</td>
<td>Imipenem</td>
<td>Cilastatin</td>
<td></td>
</tr>
</tbody>
</table>

### 6. REFERENCES


Conflict of Interest: None
Source of Funding: Nil