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Pharmacokinetic Enhancers

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OVERVIEW

Pharmacokinetic enhancers or boosting agents are used in combination with a primary therapeutic agent, not for their direct effects on the disease or condition for which they are used, but because they enhance the activity, increase drug levels and/or prolong the half-life of the primary agent. Pharmacokinetic enhancers typically inhibit enzymes such as human cytochrome P450 (CYP 3A) and thereby block the rate-controlling steps in the metabolism of the primary drug or inhibit its inactivation. While pharmacokinetic enhancers are usually well tolerated, they can be problematic and may account for side effects including liver injury of the drug combination. Furthermore, pharmacokinetic enhancers are often used as a fixed combination with the primary agent in one tablet, capsule, powder or solution for injection. For this reason, their role in causing adverse events may be difficult to define unless there are direct comparisons to subjects treated with the primary agent alone.

Pharmacokinetic enhancers in current use can be categorized into three groups: (1) beta-lactamase inhibitors used in combination with beta-lactam antibiotics such as the penicillins and cephalosporins (clavulanate, tazobactam, sulbactam, avibactam); (2) broad-spectrum inhibitors of hepatic drug-metabolizing enzymes such as CYP 3A4 (ritonavir, cobicistat); and (3) inhibitors of drug-specific metabolizing enzymes (carbidopa, cilastatin, tipiracil). Undoubtedly, other categories of pharmacokinetic enhancers will be developed as they can play an essential role in optimizing pharmacologic and therapeutic effects of important medications.

The major pharmacokinetic enhancers in clinical use in the United States are listed in the table below, along with the primary agent(s) with which they are combined, major brand name(s) of the combination, the enzyme activity that they inhibit or enhance, year of approval, and the hepatotoxicity score of the combination. Specific information and references to their hepatotoxicity are given in the sections on the primary agents rather than separately for the pharmacokinetic enhancer.

PHARMACOKINETIC ENHANCERS (2017)

Pharmacokinetic Enhancer	Primary Agent	Brand Name	Enzyme Inhibited	Year Approved	Likelihood Score†
Carbidopa	Levodopa	Sinemet	L-amino acid decarboxylase	1975	E
Clavulanic acid	Amoxicillin	Augmentin	Beta-lactamase	1984	A*
Clavulanic acid	Ticarcillin	Timentin	Beta-lactamase	1985	A*
Tazobactam	Piperacillin	Zosyn	Beta-lactamase	1985	E*
Cilastatin	Imipenem	Primaxin	Dehydropeptidase 1	1985	D
Sulbactam	Ampicillin	Unasyn	Beta-lactamase	1986	C
Ritonavir‡	Lopinavir	Kaletra	CYP 3A4	1996	D
Ritonavir‡	Paritaprevir	Viekira Pak	CYP 3A4	2015	E*

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PHARMACOKINETIC ENHANCERS (2017)					
Pharmacokinetic Enhancer	Primary Agent	Brand Name	Enzyme Inhibited	Year Approved	Likelihood Score†
Cobicistat‡‡	Elvitegravir	Stribild, Genvoya	CYP 3A4	2012	E
Cobicistat‡‡	Atazanavir	Evotaz	CYP 3A4	2015	D
Cobicistat‡‡	Darunavir	Prezcobix	CYP 3A4	2015	E*
Tipiracil	Trifluridine	Lonsurf	Thymidine phosphorylase	2015	E
Avibactam	Ceftazidime	Ayvcaz	Beta-lactamase	2015	E

† The likelihood score is for the combination, as the role of the primary agent vs the pharmacokinetic enhancer cannot always be clearly demarcated. In the case of clavulanic acid, it is usually considered the primary cause of the liver injury rather than amoxicillin or ticarcillin with which it is combined.

‡ Ritonavir is a HIV-protease inhibitor and has independent activity against HIV infection, but is used commonly to "boost" levels of other drugs active against HIV or HCV that are metabolized by CYP 3A4 and thus achieve higher and more prolonged levels when combined with ritonavir.

‡‡ Cobicistat inhibits several drug-metabolizing enzymes including CYP 3A4, CYP 2D6 and the P-glycoprotein transporter, but has no antiviral activity on its own.

Pharmacokinetic Enhancers Combined with Specific Primary Agent(s):

Avibactam [Ceftazidime], Carbidopa [Levodopa], Cilastatin [Imipenem], Clavulanic Acid [Amoxicillin, Ticarcillin], Cobicistat [Atazanavir, Darunavir, Elvitegravir], Ritonavir [Lopinavir, Paritaprevir], Sulbactam [Ampicillin], Tazobactam [Piperacillin], Tipiracil [Trifluridine]