References


Interactions of antibiotics with other drugs

There are numerous drug interactions involving antimicrobial agents—more than 120 are listed in a recent textbook (Norris & Mandell, 1985)—and it is impossible to describe each of these in detail. For ease of consideration, however, they can be broadly divided into three types; pharmaceutical, pharmacodynamic and pharmacokinetic interactions (Kristensen, 1976).

Pharmaceutical interactions occur outside the body when physicochemically incompatible drugs are mixed before administration. One of the best known is the formation of complexes and subsequent mutual inactivation that occur when carbencillin and gentamicin are mixed. Such interactions are generally preventable merely by avoiding any combination of drugs in the same intravenous infusion fluid unless compatibility is proven. Pharmacodynamic interactions depend upon opposite or additive effects at the site of drug action. They are often predictable but sometimes the interaction is an indirect one and less obvious: the effect of amphotericin B in producing hypokalaemia, for example, may alter the therapeutic effect of digoxin.

Most interactions involving antibiotics are pharmacokinetic ones and occur when one drug (the precipitant) alters the absorption, distribution or elimination (either metabolism or excretion) of another (the target drug). Antibiotics may be the targets of such interactions, especially when their absorption from the gastrointestinal tract is affected. This may result from a number of mechanisms. Alkalis affect basic antibiotics such as tetracycline; narcotics strongly inhibit gastric emptying and delay the absorption of several drugs; calcium, aluminium, magnesium and iron salts are chelated by tetracyclines (Neuvonen, 1976). Rarely, however, are any of these interactions of clinical importance.

Drugs which have a high affinity for serum albumin may cause displacement of other protein-bound drugs. As a consequence the plasma concentration of the unbound drug
rises. The small degree of displacement, however, will only elevate the plasma concentration of free drug significantly if the target in question is both very highly protein bound and also has a low apparent volume of distribution. Warfarin is one such drug and its displacement by sulphonamides and nalidixic acid leads to potentiation of anticoagulation. Tolbutamide and thiopentone may also be potentiated by sulphonamides in this way. The effects generally occur very rapidly but usually wear off over a few days. This is because the increase in free drug concentration usually leads to a compensatory increase in the excretion of drug from the body; within a few days, therefore, a new steady state is achieved with the free drug at its previous concentration, although the total drug concentration will be lower than before. The importance of these interactions is often overstressed as the patient will usually weather the adverse effects. One result, however, is that measurement of the plasma concentration of the drug (which is routinely of total rather than unbound drug), will suggest that the dose needs increasing, a response that could lead to toxicity. The correct response is to do nothing but to adopt a revised, lower, therapeutic range.

Among the most significant drug interactions are those that arise as a result of alterations in the rate of drug metabolism by the liver. Some drugs stimulate the synthesis of hepatic microsomal oxidase enzymes. This enhances the metabolism of drugs eliminated by this route and one result of this is that the drug becomes less effective. There are two antimicrobial agents that act significantly as enzyme inducers, rifampicin and griseofulvin, and the principal target drugs are warfarin, glucocorticoids and the hormonal contents of oral contraceptives. Rifampicin is a particularly potent enzyme inducer (Zilly, Breimer & Richter, 1977) and so those being treated for tuberculosis are especially likely to experience contraceptive failure (Skolnick et al., 1976) or to reject transplants because of a reduced effect of steroids (Buffington et al., 1976). A further effect of enzyme induction is seen in those drugs with toxic metabolites capable of binding irreversibly to essential cellular constituents, often in the liver. Such an interaction probably accounts for the increased isoniazid-induced hepatotoxicity that occurs when rifampicin is also administered (Timbrell, 1983).

If an inducing drug is added to an existing prescription then enzyme synthesis occurs gradually and may take a few weeks to produce maximum effect; upon withdrawal the effect will be reversed over a similar time scale. If, however, another drug is given to a patient already receiving rifampicin or griseofulvin then the effect is immediate.

Enzyme inhibition also occurs. This is usually a result of competition of the drugs for the active site of a drug metabolising enzyme (Kristensen, 1976). Inhibition leads to elevated plasma concentrations and an increased pharmacological effect, particularly if the target undergoes dose-dependent metabolism (Park & Breckenridge, 1981). Antibiotics known to act as inhibitors include erythromycin and some 4-quinolones (affecting theophylline metabolism), sulphonamides, chloramphenicol and isoniazid, (which potentiate phenytoin, warfarin and tolbutamide) and the antifungal agents ketoconazole and miconazole (affecting warfarin). Metronidazole inhibits the metabolism of acetaldehyde leading to a disulfiram-like reaction when alcohol is taken, and also causes a stereospecific inhibition of the S (-) isomer of warfarin (O'Reilly 1976).

The consequences of enzyme inhibition are often more serious than those of enzyme induction as accumulation begins immediately, even though the clinical effects may not become apparent for several weeks. When the antibiotic administration is withdrawn then the plasma concentration of the target drug will fall and upward adjustment of the dose should be anticipated.

There have been very rare reports of contraceptive failure following a short course of a broad spectrum antibiotic. They result as a consequence of suppression of the colonic bacteria: normally these are important in the enterohepatic circulation of ethinylestradiol by breaking down conjugates and releasing the oestrogen for reabsorption (Roberton & Johnson, 1976). The progestogen components of contraceptive pills are not affected. The risk of contraceptive failure during antibiotic therapy is unpredictable and so small that it is illogical to increase the oestrogen dosage while antibiotics are being taken. It does seem prudent, however, for additional contraceptive precautions to be taken during antibiotic therapy. Other effects of antibiotic killing of gastrointestinal bacteria are a reduction in the absorption of vitamin K and thus potentiation of the effects of warfarin and an increase in digoxin levels in the minority of people who inactivate large amounts of digoxin in their gut.
Many acidic drugs and their metabolites share the same active proximal renal tubular secretory pathway and their excretion may therefore be blocked by probenecid, an interaction that can be beneficially utilised (Kristensen, 1976). Gentamicin and frusemide also compete for excretion.

Pharmacodynamic interactions involving antibiotics are uncommon. Examples are the complex interactions between cephalosporins, aminoglycosides and diuretics which lead to increased oto- and nephrotoxicity, and the potentiation of non-polarising muscle relaxants by aminoglycosides, colistin and lincomamines.

The potential for interaction between antibiotics and other drugs needs to be continually borne in mind, especially with the increasing trend towards polypharmacy such that many patients are taking four or five different agents. In these circumstances even short courses of antibiotics may have serious consequences.

MARTIN J. WOOD
East Birmingham Hospital, Birmingham B9 5ST, U.K.

References


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