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Adverse Effects of Antimicrobials via Predictable or Idiosyncratic Inhibition of Host Mitochondrial Components

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This minireview explores mitochondria as a site for antibiotic-host interactions that lead to pathophysiologic responses manifested as nonantibacterial side effects. Mitochondrion-based side effects are possibly related to the notion that these organelles are archaic bacterial ancestors or commandeered remnants that have co-evolved in eukaryotic cells; thus, this minireview focuses on mitochondrial damage that may be analogous to the antibacterial effects of the drugs. Special attention is devoted to aminoglycosides, chloramphenicol, and fluoroquinolones and their respective single side effects related to mitochondrial disturbances. Linezolid/oxazolidinone multisystemic toxicity is also discussed. Aminoglycosides and oxazolidinones are inhibitors of bacterial ribosomes, and some of their side effects appear to be based on direct inhibition of mitochondrial ribosomes. Chloramphenicol and fluoroquinolones target bacterial ribosomes and gyrases/topoisomerases, respectively, both of which are present in mitochondria. However, the side effects of chloramphenicol and the fluoroquinolones appear to be based on idiosyncratic damage to host mitochondria. Nonetheless, it appears that mitochondrion-associated side effects are a potential aspect of antibiotics whose targets are shared by prokaryotes and mitochondria—an important consideration for future drug design.

SIDE EFFECTS OF ANTIBACTERIAL DRUGS

The desired activity of an antibiotic is to kill or prevent the growth of offending pathogenic bacteria, and yet these drugs may impact the host in an injurious manner. Generalized adverse events are common to most antibiotics (e.g., gastrointestinal distress with any oral antibacterial drug), but certain antibiotics are associated with specific effects (Table 1). Some adverse events are mild, e.g., yellowing of the teeth for tetracyclines (77, 79), increased intestinal peristalsis related to erythromycin therapy (7, 67), and reversible orange discoloration of skin and body fluids as observed with rifampin treatment (23, 31). Altered drug metabolism (106) is a common side effect that, in the absence of co-drug therapy, could also be considered mild. More serious side effects include photosensitivity (44) and anaphylactoid reactions (34) observed with many agents, ototoxicity (27, 83) following aminoglycoside therapy, chondrotoxicity (85, 88) and retinopathy (95) with fluoroquinolones, neuropathies associated with metronidazole (30, 107) and linezolid (15), and lactic acidosis and serotonin syndrome attributed to linezolid (21, 61). Other consequences can be severe or even devastating such as: the dermonecrotic Stevens-Johnson syndrome associated with sulfonamide antimicrobial agents (74, 81); nephrotoxicity related to aminoglycosides (63, 73); aplastic anemia due to chloramphenicol (9, 91); hepatitis caused by many drugs, including isoniazid (72, 89); neuromuscular blockade related to aminoglycoside (64, 65) or lincosamide (4, 70) therapy; myopathies due to ionophores (5, 28, 75); and neoplasia related to metronidazole (19). All of these side effects are likely to have unique etiologies given the diverse array of events, the unrelated pharmacodynamic properties of certain antimicrobial classes, and the unique chemical nature of these agents. However, as new evidence is unveiled, mitochondrial alterations form the basis for a divergent array of adverse effects observed in association with chemically distinct drugs. Mitochondrial components (e.g., ribosomes, gyrases, and topoisomerases) share little homology with prokaryotic cohorts and thus are less likely to be inhibited by antibiotics than are prokaryotic ribosomes, gyrases,

and topoisomerases (36, 47, 96, 97). However, it appears that some inhibitors of prokaryotic ribosomes, gyrases, and topoisomerases can elicit unexpected effects on mitochondria that lead to side effects of these antibiotics. Inhibition of protein synthesis, the major impetus for the antibacterial effects of rRNA inhibitors (6, 58), appears to be relevant to many of the mitochondrion-based toxicities.

AMINOGLYCOSIDES AND OTOTOXICITY

Aminoglycosides are irreversible inhibitors of the 30S, and less commonly the 50s, bacterial ribosomal subunit, thereby serving as inhibitors of protein synthesis. Most aminoglycosides are bactericidal, which is likely related to toxic peptides synthesized by the 30S subunit after the aminoglycoside-ribosome interaction. The nature of this interaction is potentially related to the electrochemical polarity of these drugs. Aminoglycosides are so polar that oral bioavailability is very poor, resulting in limited drug passage through lipid membranes in the gut. This polarity may contribute to a covalent interaction with the 30S subunit.

There has long been an association between aminoglycosides (streptomycin, kanamycin, neomycin, gentamicin, tobramycin, and amikacin) and ototoxic side effects in 20% of human patients receiving any of these drugs (17, 83). The main site of action for the aminoglycoside ototoxicity is either the cochlea or the vestibulum (62), resulting in hearing loss or dysequilibrium, respectively. There is an increase in toxicity when more than one ototoxic drug is used in combination with another. Premature infants and children may be more susceptible to ototoxicity as the inner ear develops (35). In human patients on gentamicin, those with the

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TABLE 1 Summary of side effects attributed to specific antibiotics or classes of antibiotics^a

Antibiotic or antibiotic class	Adverse effect	Basis of the adverse effect	Reference(s)
Aminoglycosides	Nephrotoxicity	Permeabilization of cells in renal proximal tubular cells	38, 94, 108
Aminoglycosides	Neuromuscular blockade	Acetylcholine receptor antagonism	48, 53
Aminoglycosides	Ototoxicity	Inhibition of the 12S ribosomal subunit in mitochondria in cochlear and vestibular cells	35, 40
Chloramphenicol	Aplastic anemia	Inhibition of mitochondrial protein synthesis, resulting in decreased expression of the transferritin receptor	39, 50, 56, 59
<i>Erythromycin (and possibly other macrolides)</i>	<i>Intestinal hyperperistalsis</i>	<i>Activation of the motilin receptor that promotes intestinal kinetics</i>	14
Fluoroquinolones	Dysglycemia	Reduced GLUT1 gene expression	1, 22
Fluoroquinolones	Orthopedic anomalies	Inhibition of DNA gyrase and topoisomerase in mitochondria in chondrocytes, osteoblasts, and tenocytes	11, 13, 51, 69, 84, 101
Fluoroquinolones	Retinopathies	Fluoroquinolones absorbing UV light and creating radicals resulting in damage to lens proteins; histological changes in the outer nuclear layer as well as the photoreceptor inner and outer segments	16, 105
Ionophores	Myopathies	Ion channel dysregulation in myocytes	5, 37, 75
Isoniazid	Hepatitis	Generation of an electrophilic metabolic that precipitates proteins in hepatocytes	57
<i>Lincosamides</i>	<i>Neuromuscular blockade</i>	<i>Acetylcholine receptor inactivation</i>	48
Linezolid (and eperezolid, another oxazolidinone)	Hyperlactatemia, myelosuppression, neuropathy	Inhibition of mitochondrial protein synthesis	21, 55, 60, 61, 87
Metronidazole (nitroimidazole)	Serotonin syndrome	Monoamine oxidase inhibition for the serotonin syndrome	
Metronidazole	Reversible neuropathy	Dentate nucleus anomalies	30, 98
Metronidazole	Neoplasia	DNA damage	19
Rifampin and other antibiotics	Orange/red discoloration of skin and body fluids	Unclear, although it may be related to bilirubinemia	31
Sulfonamides	Stevens-Johnson syndrome	Immune mediated	20, 43
<i>Tetracyclines (not doxycycline)</i>	<i>Yellowing of the teeth</i>	<i>Chelation of dental calcium</i>	77, 79
<i>Tetracyclines</i>	<i>Vestibular problems</i>	<i>Otic osmotic changes</i>	45

^a For each side effect, the mechanistic basis is listed. Alterations in drug metabolism and gastrointestinal effects are not included due to the large numbers of these events. Those involving mitochondrial damage are shaded. Ribosomal inhibitors that do not damage mitochondria are italicized.

A1555G or C1494T (less frequent) mutation in the 12S rRNA gene of the mitochondria tend to be more susceptible to ototoxicity, indicating a link to mitochondrial aberration (35). The secondary structure of the A site of the 30S bacterial ribosome is very similar to the secondary structure of the A site encompassing the human mitochondrial mutation (40). These researchers propose a molecular mechanism whereby the A1555G or C1494T mutation leads to mitochondrial 12S ribosomal secondary structures that mimic the analogous structure in the 30S bacterial ribosome. While it appears that aminoglycosides can bind to the mitochondrial 12S ribosome, it remains unclear how this interaction leads to selective dysfunction of cochlear or vestibular cells.

CHLORAMPHENICOL AND APLASTIC ANEMIA

Chloramphenicol limits bacterial growth by binding to the 50S ribosomal subunit and inhibiting protein synthesis in prokaryotes. Unfortunately, ribosomal similarities between bacteria and mitochondria (26) may provide the basis for mitochondrial sensitivity to chloramphenicol-mediated inhibition of protein synthesis. Mitochondrial DNA codes for 13 polypeptides involved in metabolic activities, and none of these genes are expressed from the nucleus (2, 3). Expression of the transferritin receptor seems to be the most relevant to the chloramphenicol-mitochondrion interaction. Specifically, chloramphenicol diminishes mitochondrion-based transferritin receptor expression, resulting in ferritin depletion in mitochondria. The resulting imbalance between organic and inorganic iron coincides with an excess of nonferritin

iron in the mitochondria of patients receiving chloramphenicol (50).

Aplastic anemia has been associated with chloramphenicol therapy for many years (10, 41), and this finding is the basis for the ban on chloramphenicol use in food-producing animals (100). Chloramphenicol-mediated hematotoxicity manifests as either a reversible (41), predictable, dose-dependent, early-onset, mild anemia characterized by reticulocytopenia with occasional leukopenia and thrombocytopenia observed during therapy (80, 92, 104) or a posttreatment pancytopenia that is unpredictable, irreversible, dose independent, and occasionally fatal (103, 104). The early-onset myelosuppression primarily affects erythropoiesis, whereby the bone marrow exhibits an essentially normal landscape of cell types with reduced numbers of maturing erythroid cells (8, 76). The latent aplastic anemia manifests as a severe pancytopenia related to an absence of myeloid constituents in the marrow (32, 99, 102).

The lipoidal nature of chloramphenicol results in a large volume of distribution that includes many "privileged" sites such as the brain and the bone marrow (42). Chloramphenicol can readily cross most cell membranes, and yet the side effects are presented in the marrow. Maturing hematopoietic cells are completely dependent upon transferritin for iron intake (68), and these cells are exquisitely sensitive to hypoferritinization. Consequently, ferritin-free mitochondria are metabolically dysfunctional, and affected erythrocytes manifest this phenomenon via hypochromic-microcytic anemia during the dose-dependent anemia associated

with chloramphenicol. Aplastic anemia appears to have ancillary factors such as underlying mitochondrial dysfunction (50), genetic polymorphisms that accentuate chloramphenicol binding to mitochondrial rRNA (39, 56), or a genetic predisposition that enhances the ability of the bone marrow to nitroreduce chloramphenicol into its myelotoxic derivative (59). That is, chloramphenicol-mediated aplastic anemia is related to mitochondrion-based alterations in ferritin but the exaggerated nature of this adverse event does not have a clearly defined basis and thus remains idiosyncratic. A nitro group, present in chloramphenicol but absent in the less toxic derivatives florfenicol and thiamphenicol, appears to be the chemical determinant of the aplastic anemia (86). Of all the mitochondrion-based side effects mentioned in this minireview, chloramphenicol-associated aplastic anemia is the only example confined to a single antibiotic within an antibiotic class. Mitochondrial disturbances have been noted for multiple drugs within the fluoroquinolone, aminoglycoside, and oxazolidinone classes.

FLUOROQUINOLONES AND CHONDROTOXICITY

A putative side effect of fluoroquinolones is chondrotenotoxicity (29) that can lead to arthropathies (93) and ruptured tendons (82). These particular side effects are mostly observed in juvenile patients (49) in whom tendons and joints are rapidly proliferating. However, this is not a clearly established phenomenon (18) but is worthy of inclusion in this review.

Fluoroquinolones are inhibitors of bacterial gyrases and topoisomerases. These drugs stabilize enzyme/cleaved DNA complexes within the cell, thus terminating DNA replication, whereby fluoroquinolone-exposed bacteria are not viable and are not able to recover once the drug is gone (54). DNA degradation has been reported in mitochondria exposed to fluoroquinolones (46), but there is no direct evidence of a link between this event and the inhibition of mitochondrial gyrases or topoisomerases. It is possible that this phenomenon is due to fluoroquinolone inhibition of mitochondrial enzymes, but mitochondrial topoisomerases bear less than 30% homology to their prokaryotic counterparts, and previous studies demonstrated that mitochondrial topoisomerases are not inhibited by nalidixic acid (47) or ciprofloxacin (71).

In vitro toxicity has been demonstrated in tenocytes and chondrocytes (11, 84, 101), and the chondrotoxicity has been associated with reactive oxygen species (51). Osteoblasts are also sensitive to fluoroquinolones, since these cells produce excess lactate in the presence of therapeutically relevant concentrations of the drug (13). No other specific cell types have been shown to be sensitive to fluoroquinolones; thus, it remains unclear why these drugs have a tropism for mitochondria in tenocytes, chondrocytes, and osteoblasts. Fluoroquinolone side effects are usually observed in juvenile patients, and thus, their developing cells may contain mitochondria that are hypersensitive to this antibiotic class (69). However, the lack of hematopoietic anomalies suggests that other factors dictate fluoroquinolone damage to tenocytes, chondrocytes, and osteoblasts.

Hyaluronic acid, which is essential for the maintenance of synovial joints, has recently been shown to have a protective effect for radical-induced mitochondrial DNA damage (25). In this scenario, hyaluronic acid may be utilized by mitochondria damaged by fluoroquinolone exposure, thereby creating a shortage of hyaluronic acid at the articular surface of the joint. This would account for the degradation of articular cartilage (78) observed in fluoro-

quinolone-associated arthropathies, but it would not account for the ruptured tendons, for which tenocyte-specific damage is the putative etiology.

The chondrotoxic effects of fluoroquinolones may not be completely due to mitochondrial disturbances. For example, there is growing evidence that these drugs sequester magnesium ions essential for integrins responsible for cell-cell adhesion (84). This has been further substantiated by the work of Pfister et al., who demonstrated that administration of magnesium and vitamin E has a protective effect for fluoroquinolone-induced chondrotoxicity in a rat model (66). Thus, fluoroquinolone-mediated chondrotoxicity probably relates to the cumulative effects of mitochondrial DNA damage, sequestration of essential cofactors, and an imbalance of chondroprotective substances. In summary, these side effects of fluoroquinolones are idiosyncratic, but mitochondrial damage is likely at the core of these toxicities.

MULTISYSTEMIC TOXICITY OF LINEZOLID AND OTHER OXAZOLIDINONES

Linezolid is a member of the oxazolidinone group of antimicrobials that inhibits bacterial ribosomes by binding to the 23S ribosome and preventing the 30S-50S fusion (52). Disruption of mammalian mitochondrial protein synthesis has been implicated in three side effects of linezolid—hyperlactatemia, myelosuppression, and neuropathies.

Garrabou et al. demonstrated that linezolid-mediated hyperlactatemia is due to the blockade of cytochrome *c* oxidase synthesis in mitochondria (21). This enzyme is the final step in the electron transport chain, and its inhibition halts a key ATP synthetic step in this pathway. This leads to a compensatory excess of glycolysis-derived pyruvate that is anaerobically converted to lactate, hence the hyperlactatemia. This same phenomenon was observed with eperezolid (60).

Nagiec et al. (60) also demonstrated that mammalian cell proliferation is hampered in the presence of eperezolid. This finding is consistent with the myelosuppressive effects of oxazolidinones whereby myeloprogenitor cell maturation is hampered (24, 90). Eperezolid has no effect on cell proliferation in rhoO cells lacking mitochondrial DNA, whereas the mitochondrial DNA-bearing parental cells (143B) were inhibited by eperezolid (60).

Linezolid-associated optic neuropathies have been reported on numerous occasions in patients receiving the drug beyond the standard 28-day regimen (reviewed in reference 33). Clinical features of these optic neuropathies are diagnostically consistent with those observed in other optic neuropathies definitively associated with mitochondrial dysfunction. A genetic predisposition seems likely since linezolid-associated optic neuropathies have been observed only in a few patients on extended-term therapy with linezolid (33). Peripheral neuropathies appear to have the same mechanistic basis as the optic neuropathies, and extended linezolid therapy underlies this condition as well (12).

In summary, oxazolidinone-mediated hyperlactatemia appears to be related to the inhibition of mitochondrial protein synthesis. Since these antibiotics are protein synthesis inhibitors in bacteria, the evidence suggests that this side effect is more predictable than idiosyncratic.

CONCLUSIONS

In summary, aminoglycosides, chloramphenicol, fluoroquinolones, and linezolid have side effects associated with mitochondrial

damage in the host. Except for neuropathies associated with linezolid, these side effects occur at doses approved for the intended clinical applications. That is, the therapeutic index (toxic dose in 50% of patients [TD₅₀]/effective dose in 50% of patients [ED₅₀]) is essentially unity for the majority of these mitochondrion-based side effects. Aminoglycoside-associated ototoxicity and linezolid-mediated hyperlactatemia do not appear to be idiosyncratic, i.e., the other side effects are based upon mitochondrial alterations but the associated changes may be “off-target” effects upon mitochondrial components unrelated to the prokaryotic component targeted by the antibiotic.

Chloramphenicol inhibits mitochondrial synthesis of a protein necessary for iron transport, aminoglycosides inhibit the 12S ribosomal subunit in vestibular and cochlear cells, fluoroquinolones cause DNA damage in mitochondria associated with joints and tendons, and linezolid inhibits cytochrome oxidase *c* synthesis in mitochondria. Three of these four drugs are antibacterial via direct prokaryotic ribosome inhibition, but a number of other ribosomal inhibitors (e.g., tetracyclines, macrolides, streptogramins, and pleuromutilins) do not appear to have side effects associated with mitochondrial damage. Additionally, aminoglycosides, chloramphenicol, fluoroquinolone, and linezolid have side effects that are not associated with mitochondrial damage—neuromuscular blockade associated with aminoglycosides, chloramphenicol-mediated alterations in drug metabolism, retinopathies subsequent to fluoroquinolone therapy, and serotonin syndrome associated with linezolid. While some of the toxicities described here are idiosyncratic, the design of new antibiotics should, nonetheless, account for potential commonalities in bacterial and mitochondria whereby preference is given to drugs that target prokaryotic pathways that are truly extant in mitochondria. Cell membrane synthesis inhibitors and inhibitors of metabolic cascades are examples of antibiotics that appear to have advantages in terms of minimizing untoward effects in patients.

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