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Antiprotozoal Drugs

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INTRODUCTION

Chemotherapy for protozoal infections continues to cause adverse effects, some at doses in their normal therapeutic index. A literature search of >4300 PubMed articles was reviewed against already published data in online pharmaceutical databases to present the contents included in this year's chapter. The inclusion of the combination of trimethoprim–sulfamethoxazole and thiamine, which are non-antiprotozoal therapies, was required as these agents were used in two clinical trials treating protozoal infections. The use of combination therapies and the correlated increase in adverse events is a recurring theme this year as investigators make advances in the treatment of protozoal infections. Phase II results of fexinidazole are included in this chapter; however, it is not currently FDA approved in the United States.

ALBENDAZOLE

Methyl *N*-(6-propylsulfanyl-1H-benzimidazol-2-yl) carbamate

Albendazole is a benzimidazole and anthelmintic agent most commonly used in the treatment of echinococcosis (also known as Hydatid cysts) and neurocysticercosis [1,2]. It causes degenerative alterations to the tegument and intestine of worms; this leads to impaired uptake of glucose and causes a depletion of glycogen stores [2]. Albendazole ultimately causes a decrease in the production of ATP which causes immobilization and death of the worm.

Drug-Interaction

The investigators of a recent trial evaluated the effectiveness of combined therapy of praziquantel and

albendazole (50 mg/kg/day and 15 mg/kg/day, respectively) in comparison to two different doses of just albendazole (15 or 22.5 mg/kg/day) in the treatment of neurocysticercosis [3C]. Praziquantel is also an anthelmintic that works by causing strong contractions within the parasite that causes paralysis and eventual dislodgment [4,5]. The purpose of the study was to determine if combining the two different mechanisms would be more effective than single agent therapy. It has also been noted in the past that praziquantel increases the serum concentration of the active metabolite of albendazole [2]. The side effects listed by the study were described as seizures, headache, pregnancy, drug-induced hepatitis, and “other” which included spontaneous abortion, urinary tract infection, motor vehicle accident, dizziness, fever, vomiting, and intracranial hypertension. While all of the side effect groups except for the drug-induced hepatitis were more common in the increased dose of albendazole or the combination therapy than in the standard albendazole therapy, the study found that the increased prevalence of adverse effects was not statistically significant. Currently, there is not a listed interaction between albendazole and praziquantel with the active ingredients of birth control.

ARTEMETHER–LUMEFANTRINE

(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-
Decahydro-10-methoxy-3,6,9-trimethyl-3,12-
epoxy-12H-pyrano[4,3-*j*]-1,2-benzodioxepin; 2,7-
Dichloro-9-[(4-chlorophenyl)methylene]- α -
[(dibutylamino)methyl]-9H-fluorene-4-methanol

Artemether is a semisynthetic derivative of artemisinin, a naturally occurring sesquiterpene lactone obtained from the Chinese herb *Artemisia annua* (qing hao) [6].

Lumefantrine is an antimalarial agent initially developed in China for treatment of *Plasmodium falciparum* mediated malaria. It is a synthetic racemic fluorene derivative (a dichlorobenzylidene) with broad schizontocidal activity, and conforms structurally, physicochemically, and mechanistically to the aryl amino alcohol group of antimalarial agents (e.g., halofantrine, mefloquine, quinine) [7]. In an open randomized controlled clinical trial comparing the efficacy and safety of three artemisinin-based combinations, the incidence of labial herpes of 3.37% occurred in the combination of artemether–lumefantrine in doses of 20 mg/120 mg respectively.

Labial herpes is also called fever blisters or cold sores. It is caused by herpes simplex virus type 1. The virus lies latent (dormant) in the body and is reawakened (reactivated) by factors such as stress, sunburn, or fever from a wide range of infectious diseases including colds [8S]. The median age of those affected was 13 years. It is thought that the adverse event reported is not due to the combination of artemether–lumefantrine; instead, it is transmitted when a child rubs their sores and then touches another person and/or through kissing [9C,10C].

DIHYDROARTEMISININ–PIPERAQUINE

Dihydroartemisinin

(3*R*,5*aS*,6*R*,8*aS*,9*R*,12*S*,12*aR*)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-ol

Piperaquine

1,3-Bis[4-(7-chloroquinolin-4-yl)piperazin-1-yl]propane

Dihydroartemisinin–piperaquine is an antimalarial combination drug. In a meta-analysis including 27 studies comparing Dihydroartemisinin–piperaquine (DHA-P) and Artemisinin-based Combination Therapy (ACT) it was found that the DHA-P patients experience less side effects such as palpitations, sleeplessness, dizziness, vomiting, or nausea. However, there was low quality evidence indicating that DHA-P could have an association with higher frequency of QTc interval prolongation [11M].

FEXINIDAZOLE

1-Methyl-2-[[4-(methylsulfonyl)phenoxy]methyl]-5-nitro-1*H*-imidazole

Fexinidazole is a 5-nitroimidazole that may be useful in the treatment of both stages of human African Trypanosomiasis, or sleeping sickness, spread through the bite of the tsetse fly carrying either *Trypanosoma brucei gambiense* or *Trypanosoma brucei rhodesiense* [12C]. A study was completed in order to determine tolerability of a variety of different dosages and formulations. A total of 154 healthy males were used in the studies [12C,8S]. Headache was the most commonly reported adverse event followed by vomiting, nausea, and diarrhea. Other, less common adverse events include: gastro-esophageal reflux disease, abdominal pain, dizziness, flushing, increased transaminases, somnolence, regurgitation, fever, palpitations, sweating, insomnia, paresthesia, myalgia, keratitis, chest pain, dysuria, asthenia, anxiety, and dyspepsia.

FUMAGILLIN

4-(1,2-Epoxy-1,6-dimethylhex-4-enyl)-5-methoxy-1-oxaspiro[2.5]oct-6-yl hydrogen decanoate

Fumagillin is an antibiotic with activity in microsporidial infection and acts to inhibit RNA synthesis [13].

Microsporidia are obligate intracellular spore-forming protozoan parasites that are acquired by multiple pathways such as ingestion, inhalation, direct contact with the conjunctiva, animal contact, or person-to-person transmission and are heavily associated in individuals with human immunodeficiency virus [8S,14].

One review of fumagillin noted that significant bone marrow toxicity, not defined, had occurred in 4 patients receiving 60 mg orally daily for 2 weeks. These effects resolved within days of treatment cessation [15R,16A].

NITAZOXANIDE

[2-[(5-Nitro-1,3-thiazol-2-yl)carbamoyl]phenyl]ethanoate

Nitazoxanide is an antiprotozoal agent most commonly used in the treatment of diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia* but can also be used to treat *Clostridium difficile* infections. It is believed that nitazoxanide works through the interference of pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential to anaerobic metabolism [17,18]. Both *Clostridium* and *Giardia* can be found in almost all surface water and have been found to be extremely resistant to the disinfectants most commonly used to make water drinkable; in order to effectively protect a population from these organisms, filtration of drinking-water is required [8S]. Even in very small amounts, these organisms can cause infection.

It has also been shown that nitazoxanide may be effective in the treatment of some viruses including influenza, parainfluenza, coronavirus, and respiratory syncytial virus through the inhibition of viral replication [19C]. When used together with neuraminidase inhibitors in cells, nitazoxanide provides a synergistic effect.

A recent, randomized clinical trial examined the efficacy of nitazoxanide at two different doses in the treatment of acute uncomplicated influenza. Patients reported a variety of different adverse events throughout the course of treatment. Some of these adverse effects can likely be ruled out due to the fact that the patients were being treated for influenza; these include: rhinorrhea, nasal congestion, sore throat, cough, headache, myalgia, fatigue, pyrexia, and sweats/chills. Others, such as bronchitis, sinusitis, and otitis may be ruled out as complications of influenza; however, nitazoxanide can cause infection. Other adverse events reported by participants in the nitazoxanide group were uncommon (reported in <2% of participants) and included diarrhea, oropharyngeal pain, abdominal pain, vomiting, abnormal liver function tests, otitis media, constipation, dry mouth, and nasopharyngitis. Chromaturia was reported in 3% of patients receiving 300mg of nitazoxanide and 4% of patients receiving 600mg. These adverse events were more common in at least one of the nitazoxanide treatment groups when compared to placebo and are not commonly associated with influenza in adults.

OXANTEL PAMOATE–ALBENDAZOLE

Methyl [5-(propylthio)-1*H*-benzoimidazol-2-yl] carbamate

Although albendazole is the drug of choice against hookworm, it shows low efficacy at treating *T. trichuria*, a helminthes transmitted from the soil.

A clinical study involving 458 patients included an incident where one child who was receiving the combination of oxantel pamoate and albendazole had a case of fever and diarrhea within 24 hours of administration [20C]. While this case may be isolated, it was worth mentioning the rare, but possible, interaction.

POSACONAZOLE

4-(4-(4-(4-(((3*R*,5*R*)-5-(2,4-Difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl)methoxy)phenyl)piperazin-1-yl)phenyl)-2-((2*S*,3*S*)-2-hydroxypentan-3-yl)-1,2,4-triazol-3-one

Posaconazole is an ergosterol inhibitor, triazole anti-fungal medication commonly used in *Candida* and *Aspergillus*, but it can also be used against Chaga's disease, also

known as American Trypanosomiasis, which is caused by *T. cruzi*. This parasite can spread through both the lymphatic system and the vasculature and eventually accumulates in the muscle and ganglionic cells, most commonly infecting the heart [21C].

Posaconazole is known to cause inflammation of the mucosal tissue, called mucositis. While mucositis is often associated with chemotherapy, it can also result from the use of ergosterol inhibitors like posaconazole. An incidence was reported regarding the possibility of developing mucositis likely leading to dryness of the mucosal tissue. During a randomized trial testing the efficacy of posaconazole for the treatment of chronic Chaga's disease involving 26 patients in each study arm, the author's noted mucosal dryness in approximately 12% of the patients taking a high dose of posaconazole and 8% in patients taking a low dose [22C]. The authors found posaconazole to be ineffective in the treatment of Chaga's disease, but could potentially be used as a suppressive agent used as adjunct therapy for anti-trypanosomal treatment.

PRIMAQUINE

(*RS*)-*N*-(6-Methoxyquinolin-8-yl)pentane-1,4-diamine

Primaquine is an aminoquinoline used in the treatment of *Plasmodium falciparum* and *P. vivax* malaria and the prevention of relapse of *P. vivax* malaria [23,24C]. Its treatment works by eradicating the infection present in tissue; it prevents relapse by eliminating the parasite present in the blood. *P. vivax* is more resistant to other treatments than *P. falciparum* which is due to a variety of reasons including: *P. vivax* has a dormant liver stage that is difficult to kill, the earlier appearance of gametocytes during infection, and the tolerance of its sporogonic cycle to low temperatures [8S]. Currently, there are no other treatments other than primaquine that is effective in killing *P. vivax* while it is in its dormant stage. While this makes primaquine the best option for the treatment of *P. vivax*, it is not used often because of the risk of acute hemolytic anemia in patients that have glucose-6-phosphate dehydrogenase (G6PD) deficiency. A review article compiled information from four different studies dating from the late 1960s to 2000 in the mass distribution of primaquine in populations that have high prevalence of G6PD deficiency [25R]. Overall, it was found that primaquine was relatively well tolerated especially when taken with food. Around 2–4% of patients experienced side effects such as headache, epigastric pain, nausea/vomiting, dizziness, anorexia, chromaturia, and black urine (a possible symptom of hemolytic anemia). The study completed in Korea found that 0.1% of the treated population experienced black urine despite a higher prevalence of G6PD deficiency. The studies conducted

in Azerbaijan and Afghanistan both reported <1% of patients that experienced changes in urine color. Many of the patients in Azerbaijan and Afghanistan have the Mediterranean variant of G6PD which is commonly associated with severe hemolytic reactions after receiving primaquine. The study conducted in Tajikistan did not report specific adverse effects, but stated that there were very few. Combined, the four studies treated millions of people and reported only a few cases of serious adverse effects, none of which resulted in hospitalization or death.

QUINACRINE

(*RS*)-*N'*-(6-Chloro-2-methoxy-acridin-9-yl)-*N,N*-diethylpentane-1,4-diamine

Prions are infectious proteinaceous particles that are thought to cause Creutzfeld–Jakob disease which is a transmissible spongiform encephalopathy [8S]. Quinacrine is an antiprotozoal drug that is also known for having inhibitory effects on prion formation. One study looked at this inhibitory effect on the prions for the treatment of Creutzfeld–Jakob disease. This study enrolled 54 patients and randomized them 1:1 comparing quinacrine vs placebo. The study found that quinacrine does not improve survival for patients with Creutzfeld–Jakob disease. Within the first two months, there was one case of severe gastrointestinal distress in a patient receiving quinacrine. Elevated liver function tests and gastrointestinal distress were the most commonly reported adverse events by patients in the quinacrine group after the initial two months of treatment [26C].

TAFENOQUINE–CHLOROQUINE

N-[2,6-Dimethoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]quinolin-8-yl]pentane-1,4-diamine
(*RS*)-*N'*-(7-Chloroquinolin-4-yl)-*N,N*-diethyl-pentane-1,4-diamine

Tafenoquine, an 8-aminoquinoline, is a synthetic analog of primaquine that has been around awhile but is just now entering phase III trials for the treatment and prevention of relapse in the case of *Plasmodium vivax* malaria. The DETECTIVE study, which evaluates use of tafenoquine used concurrently with chloroquine, and the GATHER study (anticipated), which compares tafenoquine versus primaquine, has been introduced to determine end points such as safety, efficacy, tolerability and incidence of hemolysis. Tafenoquine is not currently approved for use but has been granted breakthrough status with the FDA to expedite the process [27].

Like primaquine, tafenoquine can cause glucose-6-phosphate dehydrogenase (G6PD) deficient patients to experience an adverse effect of hemolysis [28R]. Testing for G6PD deficiencies is thus warranted prior to tafenoquine administration.

In a study of 58 healthy subjects, some common side effects include nausea (31%), vomiting (12%), diarrhea (17%), abdominal pain (9%), headache (29%), and dizziness (19%). One patient had an event that may indicate declination in visual acuity is a potential effect which spontaneously resolved. This study also indicated application site erosion (17%) where the EKG sticker was placed. This study also found the adverse effect of QTc prolongation to be clinically insignificant when administered in combination with chloroquine [24,29C].

The DETECTIVE Trial is a phase 2b study of the safety and tolerability of the combination of chloroquine and tafenoquine in a dose ranging from 50 to 600 mg for treating *P. vivax* [30C]. The study enrolled 329 patients where 69% reported adverse events. Notably, 3 patients in this study were G6PD deficient and none of which experienced hemolysis. While these results are positive, more studies would need to be considered before removing hemolysis as a potential threat in G6PD deficient patients on tafenoquine. Adverse events in the tafenoquine plus chloroquine groups (n=55) that differed from the chloroquine alone group (n=56) include headache (25% vs 37%), chills (29% vs 37%), pyrexia (33% vs 39%), nausea (13% vs 6%), asthenia (9% vs 0%), and dizziness (13% vs 9%). In the case of asthenia, it is thought that this reaction may not have been drug related. The investigators were not able to make an association with QTc prolongation and tafenoquine; however, they were defining QTc prolongation as more than 500 ms. While these adverse effects may be attributable to the use of the drug, some of them are also signs of the disease state being treated since malarial infections can cause headache, fever, as well as vomiting [27S, 8S].

THIAMINE HYDROCHLORIDE

N-(5-Acetoxy-3-acetylthiopent-2-en-2-yl)-*N*-(4-amino-2-methylpyrimidin-5-ylmethyl)formamide hydrochloride monohydrate

Thiamine hydrochloride is converted to the active coenzyme thiamine pyrophosphate by the enzyme thiamine diphosphokinase. Thiamine pyrophosphate functions in carbohydrate metabolism in decarboxylation of alpha-keto acids and in the hexose monophosphate shunt [31].

A randomized, double blind, parallel, placebo controlled trial for the treatment of falciparum malaria in

southern Laos, utilized oral thiamine hydrochloride supplementation at 10mg daily for 7 days following the standard of anti-malarial care, then 5mg daily for an additional 35 days to determine if thiamine would decrease the number of adverse events experienced by patients receiving anti-malarial treatment. Of the 630 randomized participants, 27% of the subjects were considered biochemically thiamine deficient. Three percent of participants that received thiamine experienced diarrhea at some point during the 42 days of treatment with thiamine and 25% experienced dizziness on the first day of thiamine supplementation [32C].

TRIMETHOPRIM–SULFAMETHOXAZOLE

5-(3,4,5-Trimethoxybenzyl)pyrimidine-2,4-diamine;
N1-(5-Methylisoxazol-3-yl)sulphanilamide

Doxycycline interferes with the third stage of bacterial protein synthesis. After amino acids are activated and attached to t-RNA (transfer RNA), the resulting amino acyl-t-RNA migrates to the bacterial ribosome for synthesis of proteins. Doxycycline binds to the 30S subunit on the ribosome and inhibits binding of the aminoacyl-t-RNA molecule [33,34].

Trimethoprim–sulfamethoxazole is used in the treatment of *Pneumocystis carinii* infection (called *Pneumocystis jirovecii* is a yeast-like fungus; was considered a protozoan in the past) that causes pulmonary disease in immunocompromised patients. It acts to inhibit folic acid synthesis [34].

Melioidosis, also known as Whitmore's disease, is an infection caused by the bacteria *Burkholderia pseudomallei*. This pathogen of the genus *Pseudomonas* is known to affect both humans and animals [8S].

Drug-Interaction

In a multicentered, double blinded, non-inferiority randomized clinical trial comparing trimethoprim–sulfamethoxazole to trimethoprim–sulfamethoxazole plus doxycycline for the treatment of melioidosis, three patients experienced nail bed changes as an adverse effect to combination therapy. Trimethoprim–sulfamethoxazole was administered via weight-based dosing along with doxycycline 100 mg for twenty weeks in five locations in northeast Thailand [35C]. *P. aeruginosa* paronychia has been correlated with frequent placement of the hands in water in these countries, where discoloration results from diffusion of pyocyanin into the nail bed, and therefore the interaction between trimethoprim-sulfamethoxazole in combination with doxycycline is not likely [8S].

ARTESUNATE

(3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-ol, hydrogen succinate

Artesunate is a water soluble derivative of artemisinin. It is used to treat *Plasmodium falciparum* malaria and is considered first-line therapy [8s]. It is believed to work by creating free radicals from cleaving portions of the endoperoxide bridge and may also have other damaging effects on cATP and protein folding 36 (lexicomp). Artesunate is combined with other antimalarial drugs to avoid resistance from developing and is referred to as ACT (Artemisinin-based combination therapy). One such combination is artesunate–mefloquine therapy. Mefloquine works by destroying the asexual blood form of malaria.

In an open label, single-arm study the team of Valecha et al. evaluated the pharmacodynamics, safety and efficacy of artesunate–mefloquine combination therapy for uncomplicated malaria caused by *Plasmodium falciparum*. This was a small study with as few as 77 patients who ranged between ages 18 and 55 years old with a cure rate of nearly 100% (58/59 or 98.3; 95% CI 90.9–99.9%) [37C].

Valecha et al. reported potential adverse effects from taking a combination artesunate–mefloquine therapy including toothache, pallor, and anemia among other known adverse effects [37C]. Though these findings may seem new, the authors could not determine that this adverse effect was directly related to the drug combination and ruled it out stating that, of all the adverse events recorded, the only ones they could logically associate to the drug combination was gastritis and diarrhea. Overall, the combination therapy was well tolerated by the patient population.

MEFLOQUINE

[(R*,S*)-2,8-bis(trifluoromethyl)quinolin-4-yl]-(2-piperidyl)methanol

The indication for mefloquine hydrochloride is mefloquine-susceptible *P. falciparum* and *P. vivax* infections that may cause mild to moderate acute malaria. Malarial infections caused by *P. falciparum* and *P. vivax* may be prevented with the prophylactic use of mefloquine hydrochloride. Mefloquine hydrochloride has been linked to neurological side effects (dizziness, tinnitus, and balance problems) and psychiatric side effects (hallucinations, having the feeling of anxiousness, depression, or mistrustfulness). A five year study conducted in Denmark examined the psychiatric adverse events associated with the use of mefloquine [38R]. Patients that reported possible

psychiatric side effects were assessed with SCL-90-R tool. Using the SCL-90-R, the study found clinical significance for anxiety, phobic anxiety, and depression for patients receiving mefloquine. The study found that women experienced hallucinations more often than men. The study also found that neurological side effects can become long term and sometimes even permanent side effects. As a result, the FDA has issued a black box warning about the neurological and psychiatric side effects. If a patient develops neurological or psychiatric symptoms while taking mefloquine for the prevention of malaria, the patient should discuss his symptoms with his physician and the physician should consider discontinuing the use of mefloquine and using an alternative drug [39S,40].

ACETAZOLAMIDE

N-(5-Sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide

The study of Stienlauf et al. was designed to examine the interactions between chronic medications used in the treatment of pre-existing disease states and medications used for prophylaxis in patients traveling to developing countries. The study was a retrospective cohort that evaluated mefloquine, primaquine, doxycycline, atovaquone/proguanil, fluoroquinolone antibiotics, rifaximin, azithromycin, and acetazolamide to determine if there were interactions with chronic medications. This was a large study of over 16 000 individuals. Fluoroquinolones, as well as azithromycin, were shown to most commonly have drug–drug interactions with chronic medications. About 45% of study subjects were given a preventative medication that interacted with at least one of their chronic medications. Interactions identified in about 20% of the individuals were most commonly attributed to use of acetazolamide, primaquine and mefloquine. Also of note was the presence of drug allergies in patients taking acetazolamide where 8.1% of those in the study experienced a drug allergy. Further studies are needed to verify the results, but clinicians should be aware of such interactions between medicine used for travel with chronic conditions and/or maintenance medications [41r].

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