

ADDRESSING ADHERENCE ISSUES FOR PEDIATRIC MALARIA PATIENTS

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PEDIATRIC MALARIA: A PUZZLE WORTH SOLVING

Every minute, one hundred children in Africa contract malaria. In that same minute, malaria will claim at least one child's life while leaving at least one other child disabled. The continuing pandemic of malaria in infants and toddlers has gone unsolved for decades. Despite the many efforts and some progress in global malaria prevention and eradication, this problem persists. Astoundingly, it persists despite the fact that there are drugs that cure malaria. Something is missing.

ADHERENCE IS MISSING

Patient adherence is a substantial health issue which is significantly magnified when dealing with children. Administering traditional malaria pills to children has shown to be a hardship on both the giver and receiver of the medicine. Too often, parents or guardians administering the pills have to cut and crush them, so that it is possible for small children to swallow them. Not only does this create more effort on the parents' behalf, it is also unpleasant for the children as the crushed pills bear an extremely bitter and unpalatable taste. Therein lies the need for a palatable, easily administered form of medicine. Using an Oral Dissolvable Strip (ODS) as a vehicle to deliver the medicine addresses the problems found in the traditional pill methods. By putting medicine on a strip, the medicine is palatable (through flavor-masking) and quick dissolving, therefore being more likely to actually be consumed. Additionally, the risk of having a child refuse or even spit out the medicine is greatly decreased when using a strip as an alternative to a pill.

"Drugs don't work in patients who don't take them."

-- C. Everett Koop, MD
(Former US Surgeon General)

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HISTORICAL STANDARDS FOR DEALING WITH MALARIA

Bed Nets: Areas where campaigns provide netting to keep mosquitoes from biting people while they sleep have seen a dramatic decrease in the number of malaria cases. However, bed nets do not act as a conclusive solution to malaria as they only protect when people are under them. Due to the heat in many regions, it is not uncommon for people return to their dwellings later in the evening, therefore putting themselves at risk for mosquito bites. Some reports indicate resurgence of malaria cases even in regions using bed nets. Possible reasons for this resurgence could be lack of adherence to the recommended use of the netting¹ and/or the mosquitoes are adapting by biting during non-sleeping hours². Although not a single point solution, netting remains an important part of the management of malaria.

Insecticides: Another management tool for malaria is the use of insecticides for the eradication of the mosquito. This method does work in some cases and was the foundation for eradication in the US. Current acceptable insecticides usually need to be reapplied every month or sooner, which commonly leads to non-adherence over time.³ Furthermore, insecticides interfere with produce sales, an essential part of many of these countries' economies.⁴⁵

Vaccines and medicines: Billions of dollars have been spent on research focused on the development of a vaccine to prevent malaria infection. Despite efforts, there is no vaccine available at this time for the prevention of malaria. Even vaccines that are currently in the research and development stage are both unproven and more than a decade away from being approved for use and available to the masses. Preventive medicines do exist for short-term use for travelers; however these are not practical for long term use by people living in the region.

There are several effective drug combinations that are approved by the World Health Organization (WHO) for treating patients infected with the malaria parasite. The WHO no longer recommends the use of single drugs because parasite that cause the malaria quickly become drug resistant to them. Among the combination drug treatments are only a few products that are designed specifically for pediatric use and even fewer for infant and toddler use. These products usually consist of a powder that is mixed with water or dissolvable tablets.

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STATE OF RESEARCH AT OAK THERAPEUTICS

OAK Therapeutics has taken a three-pronged approach to contributing to the eradication of malaria. Our strategy includes a pharmaceutical product for treating children with malaria, another product targeting the prevention of malaria in children and pregnant women, and a third product aiming to control the mosquito population:

Artelutrine ODS: A Pediatric Antimalarial Drug Treatment

Artelutrine ODS™ is a pediatric malaria treatment designed for use in acute, uncomplicated malaria. Artelutrine is based on a tested, World Health Organization approved, combination therapy of Artemether and Lumefantrine⁶. OAK Therapeutics has developed a parent and patient friendly, tasty, oral medicine on a fast dissolving strip (ODS). The strip is easy to administer; simply place on the tongue or along the side of the cheek and allow it to melt or it can be chewed. The packaging for this product is specially designed to provide the drugs with added protection from the tropical environment, and also uses colors and images to assure that age-appropriate medicines are given to the child.

Development of Artelutrine ODS™: According to the WHO, the most effective treatment for malaria is an Artemisinin Combination Therapy (ACT). OAK uses one of the favored combinations, Artemether and Lumefantrine. The prescribed treatment is to administer the drugs twice a day for three consecutive days. One of the challenges for administering the six doses becomes adherence. Patients have increasing resistance to take tablets, and the fatigue it creates for the caregiver can add to lack of adherence. Artelutrine ODS™ is designed to reduce the barriers to adherence by applying proprietary masking techniques and proprietary strip construct blends. The result is a product that:

- Dissolves quickly in the mouth or. Quick dissolving in the mouth lessens the time the drug stays in the mouth that improves the taste experience and lowers the risk of spitting out the drugs.
- Quickly sticks to the tongue or cheek. Adding muco-adhesion to the strips also reduces the risk of the child spitting out the drugs, and it reduces the minimal possibility of the strip becoming a choking hazard. Furthermore, the muco-adhesive property of the strip allows it to be administered regardless of the patient's state of consciousness.

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- Has a pleasant enough taste that the patient is cooperative and the caregiver is not burdened with administering something unpleasant. For safety reasons not all the “medicine” taste is masked to ensure the strips are not confused with candy.

Drug approval: The current product has been tested for stability however the clinical studies to validate the bioavailability using the delivery system have not been conducted yet due to funding constraints. There is a pre-clinical scheduled to start in March 2015. The data from the pre-clinical study will be used to support application for regulatory permission to conduct human studies.

The estimated cost of the necessary studies is \$US 190,000.

Anbactra ODS: A Seasonal Malaria Chemoprevention Treatment

The Seasonal Malaria Chemoprevention⁷, a WHO sponsored initiative aimed at protecting small children and pregnant women from contracting malaria during high risk (rainy) seasons in Sub-Saharan Africa. Studies⁸ have shown that the two active antibiotic ingredients in Anbactra, namely Trimethoprim and Sulfamethoxazole, are effective as a chemoprevention (prophylaxis) treatment.

Development of Anbactra ODS™: Oak Therapeutics is collaborating with the Children’s Hospital of Los Angeles (CHLA) to develop and test an oral dissolvable Anbactra strip for prophylactic use for infection prevention in immune-compromised, pediatric cancer patients during and post cancer-related chemotherapy treatment.

Using criteria similar to that used with Artelutrine, Anbactra ODS™ is designed to reduce the barriers to adherence by applying proprietary masking techniques and proprietary strip construct blends. The resulting strip also has similar properties to Artelutrine:

- Dissolves quickly in the mouth or.
- Quickly sticks to the tongue or cheek.
- Has a pleasant enough taste that the patient is cooperative but still maintaining some “medicine taste” to prevent confusion of the medicine with candy.

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Drug approval: Discussions are underway with the FDA to determine the appropriate studies needed for Regulatory Submission and subsequent approval. The anticipated result would be a requirement for a bioequivalency/safety study (PK-PD) first as a clinical pilot study in healthy adults followed by a clinical study in hospitalized children.

Estimated cost of these two studies is \$US 250,000.

Ivermectin ODS: A Vector Control Treatment

Recent reports⁹ have suggested that the anthelmintic medicine, Ivermectin, may be effective in killing or sterilizing female anopheles mosquito. The female anopheles mosquito is the carrier for the malaria parasite. Controlling the mosquito population will reduce the transmission of the malaria parasite and thus the number of malaria infections.

Development of Ivermectin ODS : Oak has created an Ivermectin ODS product as part of a collaborative project with the School of Pharmacy at the University of Southern California (USC). Further work on the malaria application of the Ivermectin ODS is pending resources and funding. A joint application for an SBIR grant is in progress.

Drug approval: There are no specific plans in place at this time for getting this product through the Regulatory approval process.

There are no cost estimates for the project at this time.

Please send inquiries concerning this paper

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¹http://www.nytimes.com/2015/01/25/world/africa/mosquito-nets-for-malaria-spawn-new-epidemic-overfishing.html?_r=0

²http://www.eurekalert.org/pub_releases/2015-01/uom-bna011615.php

³<http://consumer.healthday.com/diseases-and-conditions-information-37/malaria-news-459/malaria-prevention-lancet-release-batch-1502-694396.html>

⁴<http://www.medicalnewstoday.com/articles/287907.php>

⁵<http://www.scientificamerican.com/article/ddt-use-to-combat-malaria/>

⁶http://apps.who.int/iris/bitstream/10665/93143/1/EMLc_4_eng.pdf?ua=1

⁷http://www.who.int/malaria/areas/preventive_therapies/children/en/

⁸http://www.who.int/hiv/topics/arv/cotrimoxazole_factsheet_dec2014/en/

⁹ Ivermectin as a Complementary Strategy to Kill Mosquitoes and Stop Malaria Transmission? Clin Infect Dis. first published online November 19, 2014 doi:10.1093/cid/ciu802

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