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Combination Antimalarial Therapies in Children From Papua New Guinea

ANTIMALARIAL THERAPIES IN CHILDREN IN PAPUA NEW GUINEA

Change and challenge is in the wind as 2008 comes to an end. The same is true when examining this month's ReachMD XM160 special series Focus on Global Medicine. We take a look at both the changes and the challenges impacting global medicine.

Malaria control is difficult where there is intense year around transmission of multiple species. What do the results from the life of clinical trial in Papua New Guinea tell us about treating this disease?

You are listening to ReachMD XM160, The Channel for Medical Professionals. Welcome to a special segment Focus on Global Health. I am Dr. Mary Leuchars, your host and joining me today from Perth, Australia is Dr. Tim Davis. Dr. Davis is Professor of Medicine at the University of Western Australia. Today, we are discussing the results from his clinical trial published in the life of New England Journal of Medicine, a combination antimalarial therapies in children from Papua New Guinea (OPNG).

DR. MARY LEUCHARS:

Welcome, Dr. Davis.

DR. TIM DAVIS:

Hi there.

DR. MARY LEUCHARS:

Now can you tell me why you and your colleagues chose PNG for this particular trial?

DR. TIM DAVIS:

Well, PNG is a country where the transmission of malaria is very intense and there are multiple species and in that situation the people

at risk of complications and death in young children and pregnant women and clearly there are groups that you want to protect from the effects of the infection. It's also a country, which has limited healthcare facilities, availability of drugs, and personnel to treat people with malaria is very limited. The country is mountainous apart from on the coast and even on coastal areas there are quite remote communities. So, malaria presents a big challenge in terms of its control and treatment at a community level.

DR. MARY LEUCHARS:

You mentioned that there are multiple species of malaria in Papua New Guinea. Can you give me the breakdown of the types?

DR. TIM DAVIS:

Well, obviously the most serious one is Plasmodium falciparum, which has a potential to kill people and cause complications such as cerebral malarial chyma.

DR. MARY LEUCHARS:

What percentage of patients in PNG have that type of malaria?

DR. TIM DAVIS:

That would be the majority of cases, especially in the areas in which we work on the North Coast of the island, but there is also very brisk transmission of Plasmodium vivax. Now whether that is regarded as a benign malaria we are learning more and more of that it can produce complications and even contribute to fatalities and we are recognizing; for example that repeated vivax infections can predispose to chronic anemia and that on its own can cause quite significant morbidity.

DR. MARY LEUCHARS:

What sort of drug resistant to malaria exists in PNG?

DR. TIM DAVIS:

Well the conventional drugs like chloroquine and Fancidar, sulfadoxine, pyrimethamine combination – they have been used for some time now and where chloroquine has been used for many years you get a situation where it doesn't work terribly well. In communities where there is brisk transmission immunity starts to develop, but it's not a sterilizing immunity. It's only semi-immunity and it takes some years to develop. So that's why the young children and the pregnant women are much at risk of treatment failure and the WHO of recent years has recognized that conventional therapies like chloroquine and Fancidar are no longer the answer and has recommended that we use artemisinin based combination therapies as an alternative. Now, artemisinin, I don't know if your listeners know much about these drugs, but they are Chinese herbal derivatives from the wormwood plant. They have been used for thousands of years to treat fever and about 30 years ago or more, Chinese chemists isolated the active ingredient, artemisinin and have produced a couple of semi-synthetic derivatives one of which is artemether, another one of which is artesunate and they are very, very effective at getting rid of parasites quickly from people with any form of malaria and the problem with these drugs is that although they are very good at initial treatment, they are less good at keeping the infection away and stopping later recurrences. So, WHO recommends that these drugs are

combined with something else with a longer half life that improves cure rates and hopefully protects the drug against the parasite developing resistance to it and one of the combination therapies it has recommended is something called Coartem, which in the west is known as Riamet and that's the combination of artemether and Lumefantrine. Lumefantrine is another Chinese drug that's a bit like mefloquine or Lariam and another one Artescan, which is another artemisinin derivative. This one's got a longer name, dihydroartemisinin and that's combined with a chloroquine-like drug called piperazine, which was also developed by the Chinese. So, most of the artemisinin combination therapies have come from Chinese drugs, but they are very effective and the WHO now recommends that they use first line in countries with Plasmodium falciparum as the predominant species. That having been said, chloroquine-resistant vivax malaria is an emerging problem and was actually first described in the 60s in Papua New Guinea and there are areas of the world such as PNG where you frequently see treatment failure with drugs like chloroquine and the artemisinin combination therapies can be used against vivax in this situation. So, the same clinical trial was that we knew that chloroquine in this case combined with Fancidar was a 3-drug treatment, was failing, that there were children, who were not responding who were getting recurrent infections and presenting well for retreatment and we were also aware that the WHO were wanting to recommend artemisinin and combination therapies, but we needed the information before the Crofton administrative hassle associated with them and countrywide challenge of treatment could be justified, so that's why we did the trial.

DR. MARY LEUCHARS:

Dr. Davis, when did this trial take place?

DR. TIM DAVIS:

Well, it took place between 2004-2007. We were working in 2 areas on the North Coast of PNG, one in the place called the Sepik, which is a little bit west of African side, which is very near the original center of Madang and there are 2 areas where we see a lot of childhood malaria and where we know that chloroquine and Fancidar resistance is well established. So, we screened almost 3000 children between the ages of 6 months and 5 years and there was certain entry criteria to get into the trial that couldn't be treated with any of the study drugs that had to have a detectable and reasonable level of parasites in the blood that had to have a history of fever in that sort of condition and we ended up with about 750. About two-thirds of those had falciparum malaria and about a third had vivax and we assigned them to one of the conventional treatment with chloroquine, Fancidar or to Coartem or to Artescan and or to artemisinin combination therapies as mentioned and we also had an arm where we gave artesunate, one of this artemisinin drugs with Fancidar as another way of trying to combine an artemisinin derivative with a well-tolerated and conventional therapy. So, we had 4 arms in each of the 2 species. We gave the children treatment after the diagnostic confirmation and assessment to make sure they didn't have any complications and then we tracked them over 42 days with regular assessments and we assessed them with clinical examination including an axillary temperature and also did a blood smear to see whether the parasites had returned. So, that's the basic study design, that's the one that the WHO recommends and where we found a recurrent falciparum malaria on a blood smear with or without symptoms, we would then do molecular analysis to try and estimate whether this was a new infection or whether this was the original infection having come back and that's got an important differentiation because obviously a new infection does not necessarily mean treatment failure whereas if that parasite on a molecular level seems to be the one with which the child originally presented, then that is pretty good evidence that the drug combination has failed. So, that's the basic study design.

DR. MARY LEUCHARS:

Now, what were the results of the study?

DR. TIM DAVIS:

Well, we are expecting that the 2 artemisinin combination therapies would give us cure rates probably greater than 95% at 42 days and

that the chloroquine Fancidar would probably give us a treatment success rate the way you have sent a failure rate of 20% at 42 days. The artesunate Fancidar we put that in because some people would argue that it's probably a bit cheaper therapy than the other two ICTs and we were expecting a sort of intermediate failure rate with that combination therapy. In the end, we did find that the chloroquine Fancidar had the lowest treatment success rates in the Falciparum patients, that was again a low rate well below the 95% cut point where you really need to have to continue using the therapy. Artemether, Lumefantrine, or Coartem was the best at 42 days that had a 95.2% treatment success. Much to our surprise the Artecan, the dihydroartemisinin and piperazine was not as good as we thought; it was below the 95% in fact it was 88% at 42 days. This was a bit of a surprise to us given how good the drug combination had been in a variety of other endemic countries. The artesunate Fancidar combination therapy was about 85% successful at the 42 days and the chloroquine Fancidar was the lowest. So, that seemed to support what the WHO was recommending that Coartem was a good choice for falciparum malaria, but we were surprised by the relatively low success rate of the Artecan ICT treatment and again there was enough data there for us to suggest to the PNG health authorities, which they have not done that chloroquine Fancidar should be dropped from their treatment regimen and Coartem adopted. Now with vivax the story was quite different. A lot of children got vivax malaria during followup and with this parasite, we can't really determine based on current methods with the parasite we are looking at in the followup period is the same as the one at time of treatment or whether it's a new infection. So, we can't differentiate with some reinfections, but about a third of children in the Artecan group, which was the most successful treatment for vivax malaria redeveloped vivax malaria during the 42 days, and this failure rate was double in the other 3 groups including Coartem. So, most children with Coartem redeveloped vivax malaria during followup and although a lot of these cases were not clinical failure, the children well didn't have fever, there were parasites on the blood smear and they can contribute to complications such as anemia and chronic ill health. So in this area although you might say that Coartem is indicated because it has the highest activity against the potentially lethal falciparum malaria, it wasn't very good against the vivax malaria in the area. Artecan, the other ICT was not all that good against falciparum, but was the best by quite a long way against vivax. So, quite a complex set of findings and ones that suggest that we need to look at other therapies because there is no single treatment or combination treatment that fits the epidemiological circumstances.

DR. MARY LEUCHARS:

My thanks to Dr. Tim Davis for being our guest today. We have been discussing the results of his clinical trial of combination antimalarial therapies in children in Papua New Guinea.

I am Dr. Mary Leuchars. You have been listening to a special segment focused on global medicine on ReachMD XM160, The Channel for Medical Professionals. Thank you for listening.

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