Pharmacogenetics in Africa, an Opportunity for Appropriate Drug Dosage Regimens: on the Road to Personalized Healthcare

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The modern human appeared in Africa around 200,000 years ago with subsequent later migrations to populate Europe, Asia, and North America.1 As humans adapted to various diets, diseases, climates, and so on, inherited traits emerged that gave rise to distinct population groups with physical and physiological differences, including the response to xenobiotic challenges (Figure 1). This Perspective highlights the interpopulation differences in response to drugs focusing on Africa and implications for global pharmacometric studies.

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VARIATION IN DRUG METABOLISM AND DISPOSITION

Approximately 60 years ago, the metabolism and disposition of isoniazid, an antituberculosis drug, was one of the earliest demonstrations of pharmacogenetic differences in drug handling that resulted in clinical consequences.2 There were marked differences in excretion of the drug among individuals who were then classified into slow acetylators (SA) and rapid acetylators of isoniazid with SA individuals being more prone to suffer from isoniazid-induced peripheral neuropathy. After the cytosolic enzyme, N-acetyltransferase 2 was cloned, many genetic variants were found that explained the rapid acetylators and SA status, and epidemiological studies showed that the SA status could vary from 5 to 95% depending on the population studied.2 Since the discovery of differences in extent of excretion of isoniazid, a vast literature has developed documenting many other genetic polymorphisms for drug metabolizing enzymes and drug transporters. Many of these genetic polymorphisms are known to have clinical effects and to exhibit interethnic differences (Table 1). Studies are now including pharmacogenetic variables in optimizing the clinical use of some drugs; for example, Azuma et al.3 recently conducted a randomized controlled trial for pharmacogenetics-based therapy and showed that a NAT-2 genotype–guided regimen reduces isoniazid-induced liver injury and early treatment failure in tuberculosis patients. To ensure translation of research to the bedside, the Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network is working to establish guidelines for clinical use of pharmacogenetic data.4

The clinical importance of pharmacogenetic traits has made major drug regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency develop policy documents and guidelines on the subject that can be found through a search of their world-wide websites. The pharmaceutical industry has also formed the Industry-Pharmacogenomics Working Group (www.i-pwg.org) to work on research and ethical guidelines on the integration of pharmacogenetics in drug discovery, development, and clinical use of medicines. Many drugs now carry pharmacogenetics information in their labels or leaflets, and the US Food and Drug Administration has since approved a number of pharmacogenetics tests that could be used to improve the use of these drugs (www.pharmgkb.org).

AFRICA’S GENOMIC DIVERSITY, OPPORTUNITY FOR ADVANCES IN APPROPRIATE DOSING REGIMENS, AND PERSONALIZED HEALTHCARE

The discovery of most pharmacogenetic traits was at the interindividual level followed by studies that also demonstrated interpopulation differences, reflecting the genomic diversity of populations. These observations create an interesting link between genomic medicine and recent molecular evolution arising from population/environmental factors unique in time and geography and which have implications for the safe and efficacious use of drugs in different populations (Figure 1). Most dosing regimens are recommended on the basis of clinical trials that have been done in Caucasian or Asian populations and that may not be appropriate for African populations.

The first major observation of clinical relevance for a genetic difference for Africans in safety and efficacy of a drug was for the deficiency of glucose-6-phosphate dehydrogenase, which is common in African populations and which is postulated to have arisen due to pressure from malaria infection. People with glucose-6-phosphate dehydrogenase deficiency are more resistant to malaria infection. However, should such people succumb to malaria, treatment with primaquine triggers hemolysis, as the deficiency of this enzyme compromises their ability to detoxify reactive metabolites generated from this drug (reviewed in ref. 2).

The use of isoniazid for the treatment of tuberculosis is widespread in Africa where this disease is the leading cause

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of death among HIV/AIDS patients. Southern Africa is the epicenter of the HIV/AIDS pandemic and of the tuberculosis epidemic with >50% of people with tuberculosis also being HIV positive according to WHO estimates (http://www.who.int/hiv/topics/tb/data/en/index.html). The genetic polymorphism of NAT-2 resulting in the SA and rapid acetylators status has implications for the use of isoniazid in Africa. As ~50% of African people are SA, the burden of peripheral neuropathy can be very high if the doses of the drug are not titrated against the patient's capacity to remove the drug. A further genetic polymorphism affecting the pharmacokinetics of a drug for tuberculosis, rifampicin, is that for the organic anion-transporter polypeptide 1B1 coded for by the gene SLCO1B1, which has a C/T variation (rs4149032) associated with reduced rifampicin blood levels. Pharmacometric modeling and simulation showed that for patients bearing this variant, an increase in rifampicin dose would be necessary to achieve therapeutic concentrations in the blood. The polymorphisms of NAT-2 and SLCO1B1 are therefore important for efficacious treatment of tuberculosis since isoniazid and rifampicin are components of the combination therapy for the disease.

| Gene/protein | Allele | Functional status | African | Asian | Caucasian | Some drugs affected | Clinical PK and PD effects | Interpopulation differences |
|--------------|--------|-------------------|---------|-------|----------|--------------------|---------------------------|---------------------------|
| CYP2D6       | *4     | No activity       | 1–8     | 1     | 12–21    | β-Blockers, antide pressants, dextromethorphan codeine | Tardive dyskinesia from antipsychotics, loss of therapeutic effect | African and Asian populations have lower rates of metabolism of CYP2D6 substrate drugs than Caucasians |
|              | *5     | No activity       | 1–7     | 6     | 4–6      | | | |
|              | *10    | Reduced           | 2–6     | 50    | 1–2      | | | |
|              | *17    | Reduced           | 14–34   | 0     | 0        | | | |
| CYP2C9       | *2     | Reduced           | 1       | 0     | 8–13     | Warfarin, tolbutamide, Losartan, acenocoumarol | Hemorrhage | *2 and 3 not diagnostic in Africans and Asian |
|              | *3     | Reduced           | 0       | 2–3   | 7–9      | | | Possible lower doses required in Africans with these alleles |
|              | *5, 6, 8, 9 and 11 | Reduced | –     | –     | –        | | | |
| CYP2C19      | *2     | No activity       | 13–25   | 23–32 | 13       | Omeprazole, proguanil diazepam | Increased efficacy of omeprazole, potential reduced effects of proguanil | Asians require lower doses of substrate drugs & risk reduced efficacy of proguanil |
|              | *3     | No activity       | 0       | 6–10  | 0        | | | |
| CYP2B6       | *6     | Reduced           | 34–49   | 16–21 | 15–21    | Efavirenz, artemisinin, nevirapine, cyclophosphamide | Increased CNS side effects to efavirenz | Increased ADRs reactions in African populations |
| CYP3A5       | *3     | No activity       | 20–27   | 80    | 93       | Ticagrelor, quinine atazanavir | No data | Africans could metabolize these drugs faster |
| NAT-2        | *5     | SA                | 20–58   | 5     | 20–58    | Isoniazid | Hypersensitivity to sulfonamides, isoniazid neurotoxicity | Frequency of SA in African, Asians, and Caucasians is 50, 20, and 50%, respectively |
|              | *6     | SA                | 8–29    | 19–31 | 27–28    | | | |
|              | *7     | SA                | 2–6     | 10–16 | 2–4      | | | |
|              | *14    | SA                | 3–13    | 0     | 0        | | | |
| OATP1B1      | *1B    | Increased         | 77      | 63    | 26       | Statins | Myopathy and rhabdomyolysis | Asians use lower dose of rosuvastatin than Caucasians |
|              | *5, 15 | Decreased         | 2       | 10–15 | 15–20    | | | |
| BCR          | C421A  | Decreased         | 2–5     | 35    | 11–14    | | | |
| G6PDH        | Many variants | Reduced to no activity | 15–38 | 8 | 0–10 | Primaquine, chloroquine | Hemolytic anemia | African people more susceptible to primaquine toxicity |
| HLA          | HLAB*5701 | Human leukocyte antigen | 0.26–3.6 | 0.26–3.6 | 5–8 | Abacavir | Predicts abacavir hypersensitivity |
| VKORC1       | 1173 C>T | Vitamin K regeneration | 9–24 | 74–89 | 36–42 | Warfarin | Predicts warfarin dose | Most important for Asians |

ADRs, adverse drug reaction; CNS, central nervous system; G6PDH, glucose-6-phosphate dehydrogenase; OATP1B1, organic anion-transporter polypeptide 1B1; PD, pharmacodynamic; PK, pharmacokinetic; SA, slow acetylator.

*Allele frequency data obtained from ref. 5. †CYP2C9 reviewed in ref. 10.
that patients homozygous for the low enzyme activity CYP2B6 variant would require a third of the current standard dose of 600 mg a day. Anecdotal clinical reports of patients whose central nervous system side effects resolved upon dose reduction to 200 mg a day support this predicted safe dose. With 20% of the African people being homozygous for the slow allele, CYP2B6*6, use of a dosing algorithm guided by inclusion of pharmacogenetic data could translate to a more reduced enzyme activity in African populations.8

The enzyme CYP2D6 metabolizes over 20% of drugs that are subject to metabolism by P450 and is of particular importance for the metabolism and disposition of psychoactive drugs and β-blockers. Early phenotyping studies showed a generally reduced enzyme activity in African populations. Molecular genetic studies led to the discovery of the CYP2D6*17 genetic variant as the major cause of this diminished enzyme activity.9 There is a need for clinical studies in African populations to understand the implications of using Caucasian-based dose regimens for CYP2D6 substrate drugs in patients of African origin.

THE FUTURE OF PHARMACOGENETICS IN AFRICA

The few examples cited above illustrate the way in which particular common pharmacogenetic traits can influence the safety and efficacy of drugs in Africa and highlight the critical need to ensure that dosing recommendations are made with consideration of the pharmacogenetic profile of populations as a whole and of individuals. The clear differences among African, Asian, and Caucasian populations demonstrate the need for population-specific preclinical and clinical studies and trials.

There is currently a limited capacity for pharmacogenetics and pharmacogenomics research in Africa. Strategies and policies for development of science and technology must ensure a future where Africa can take an active role in harnessing the power of genomic research in addressing its healthcare challenges. Already very positive steps are being taken with the establishment of initiatives such as the Human Heredity and Health in Africa project (http://h3afrika.org) that aims at strengthening research capacity for genomics in Africa. Another such initiative, sponsored by WHO and United Nations Economic Commission for Africa, is the African Network for Drugs and Diagnostics Innovation (http://www.andi-africa.org) whose primary objective is to promote and support health product research and development led by African institutions for diseases of high prevalence in the continent. Formation of the African Society of Human Genetics and the African Pharmacogenomics Consortium also demonstrate an increased interest and participation by African researchers in genomics research.

Pharmacogenetic/genomic studies require good pharmacological data to explore genotype and phenotype associations. To explore these associations and translate them to clinically relevant models, pharmacometric studies will play a crucial role. The challenge now is to educate and promote a cadre of trained young, energetic, and committed young scientists in Africa who will lead the continent in drug discovery and development in a global world, leading to population-appropriate pharmacology and personalized medicine. The future for exciting research in pharmacogenetics and pharmacometrics in Africa looks enticing and has great potential for translation into clinical applications in the treatment of major epidemics such as HIV/AIDS and tuberculosis, and for innovative treatment of the growing problem of noncommunicable diseases.

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