

## FIRST REPORTS OF CLINICAL PHARMACOKINETICS IN NIGERIA

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**SUMMARY**

*The German Friedrich Hartmut Dost (1910 – 1985) introduced the word Pharmacokinetics. Clinical pharmacokinetics is the direct application of knowledge regarding a drug's pharmacokinetics to a therapeutic situation in an individual or a population. It is the basis of therapeutic drug monitoring with the ultimate goal of keeping drugs safe. This branch of pharmacology has become the most relevant to the sub-specialty of clinical pharmacology. First reports of Clinical Pharmacokinetics in Nigeria can be credited to two gifted Nigerians, Prof Ayodele O. Iyun and Prof Lateef A. Salako, both of whom were affiliated to the great institutions- University of Ibadan (UI) and the Teaching Hospital, University College Hospital (UCH). Prof A.O Iyun was Nigeria's first home-trained Clinical Pharmacologist, while Prof L.A. Salako played a most significant role in the creation of the Department of Clinical Pharmacology, UCH. This edition of the Chronicles highlights a few of the first reports of this exciting branch of pharmacology in Nigeria. This historical review is based on publications listed on the United States National Library of Medicine database (PUBMED).*

**The Early Years of Clinical Pharmacokinetics (1910 – 1976)**

Science is largely close and reproducible examination of relationships between physical phenomena. It was by looking at the relationship between electricity and magnetism and the relativity of their effects that scientists created a whole revolution in scientific thinking, leading from Michael Faraday to Albert Einstein. The relationship between phenomena and time has a very long history. The word 'kinetic' refers to movement, displacement, usually in relation to time or space.

About seven decades ago, pharmacologists started examining the relationship between administered drugs, blood or plasma concentrations, and time. Friedrich Hartmut Dost (1910 – 1985) first introduced the word pharmacokinetics in 1953; however, some of the subject matter has already been published.<sup>1</sup> Dost was a German pediatrician who used mathematical calculations to optimize drug doses in children. The purpose of pharmacokinetics is to study the time course of drug and metabolite concentrations or amounts in biological fluids, tissues and excreta, and of pharmacological response, and to construct suitable models to interpret such data. In pharmacokinetics, data are analyzed using a mathematical representation of a part or the whole of an organism. His studies opened a new way of thinking of drug concentrations and optimization of therapies in every aspect of clinical

pharmacology. In remembrance of him, the German Society for Clinical Pharmacology hosts an annual award, the Friedrich-Hartmut-Dost Memorial Prize, to promote clinical pharmacology in the European countries.

**Friedrich Hartmut Dost**

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Clinical pharmacokinetics is the most important subject in the curriculum of Clinical Pharmacology. It is the direct application of knowledge regarding the pharmacokinetics of a drug to a therapeutic situation

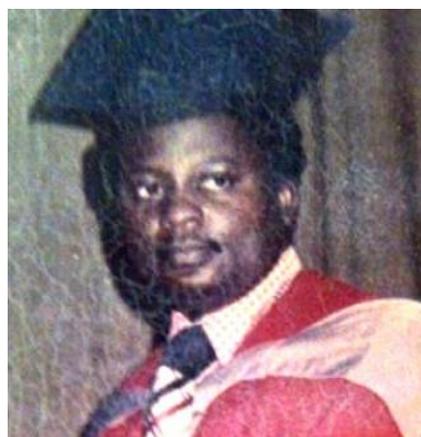
in an individual or a population. It is the basis of therapeutic drug monitoring with the ultimate goal of keeping drugs safe. Initial studies of the subject were published in journals of physiology and biochemistry. From Germany, in 1913, Michaelis and Menten published what is now known as the Michaelis-Menten equation for describing enzyme kinetics. In pharmacokinetics, this same equation is used to describe the elimination kinetics of ethanol, salicylate, phenytoin and several other drugs.<sup>2</sup> Other early workers who moved the field forward were the Swedish investigators Widmark and Tandberg (1924), and the American Haggard (1924). Moller, Jolliffe, Smith, and Hamilton introduced the concept of renal clearance and basic mathematical equations relevant to the field (1929 – 1935). Clinical pharmacokinetics was fully established in the period between 1929 – 1950. In 1976, the journal *Clinical Pharmacokinetics* was founded. The first studies of Clinical Pharmacokinetics in Nigeria were due largely to two gifted medical doctors; Prof. Ayodele Oluremi Iyun and Prof Lateef A. Salako.

#### **Prof Ayodele Oluremi Iyun (1976 – 1989)**

Prof Iyun was born in Lagos on 20 March 1944. He attended Princess School, St. David School and Lagos Government School before proceeding to King's college, Lagos from 1957 – 1961. He undertook Higher School Certificate course at Federal School of Science, Onikan, Lagos from 1963 – 1964. All through his career, he excelled in all the courses he took. He was admitted into the University of Ibadan in 1965 where he obtained the MBBS degree in June 1970. He was the first UCH resident doctor to obtain both the Master of Medicine degree and the Nigerian Fellowship in Physic (FMCP) in June 1977. In November 1978, he was awarded the Fellowship of the West African College of Physicians. His highly distinguished career was full of many firsts; he started research that can be considered today as the first reports of Clinical Pharmacokinetics in Nigeria.

In 1979, Prof Iyun defended his thesis for the FMCP fellowship titled *Pharmacokinetic Studies in Hypertensive Patients*. This was followed by a brilliant career with the University of Ibadan and University College Hospital, Ibadan, where he went on to make significant contributions to Clinical Pharmacokinetics. In 1982, Iyun and Tucker described Antipyrine kinetics in Nigerian women in chronic renal failure. He found that the mean plasma antipyrine half-life in patients with chronic renal failure was significantly shorter than in normal subjects. The results suggested that oxidation of antipyrine by hepatic microsomal enzymes is increased in patients with chronic renal failure.<sup>3</sup> By measuring plasma metoprolol concentration, Iyun and

colleagues in 1986 described the role of genetic polymorphism in the oxidative metabolism of metoprolol and debrisoquin. He concluded that in ethnic studies of drug metabolism each racial group should be examined separately for evidence of polymorphic metabolism and antimodes should not be extrapolated from one population to another.<sup>4</sup>



Prof. AO Iyun

In 1988, Iyun and colleagues evaluated the pharmacokinetics of digoxin in eight healthy volunteers, 23 congestive cardiac failure, and 10 chronic renal failure patients. They found that the mean serum digoxin concentrations in the volunteers and the congestive cardiac failure patients were significantly different from those in the chronic renal failure patients. They also found that the mean half-life of digoxin in the healthy volunteers (37.2 h +/- 8.6 s.d.) was comparable to the widely accepted 40 h for digoxin half-life in normal individuals. He recommended that in the absence of renal impairment and hypokalaemia, standard dosages of digoxin could be used in congestive cardiac failure patients, provided symptoms and signs of toxicity are constantly monitored. Iyun also recommended that therapeutic drug monitoring of digoxin is desirable in view of its low toxicity: therapeutic ratio, and its kinetics should be studied in detail in each community to establish correct dosages to prevent and manage digoxin toxicity.<sup>5</sup>

Nadolol is a non-selective beta-blocker used in the treatment of hypertension and long-term management of angina pectoris. The drug is 30% bound to protein and has a half-life of 14 – 24 hours. Side effects include dizziness and fatigue. In 1989, Prof Iyun and colleagues reported clinical experience with nadolol in Nigerian patients with essential hypertension.<sup>6</sup> Although the study did not report measurement of Nadolol concentrations over time, Iyun closely observed changes in cardiovascular parameters over time. He discovered that Nadolol was highly effective in 15 patients (65.2%) moderately effective in 6 patients

(26%) and ineffective in 2 patients (8.6%). He also stated that side effects were not a problem in this study and tolerance to the drug was excellent in most cases. At about this time Prof Iyun had started collaborating with another brilliant medical scientist, Prof Lateef A. Salako.

#### **Prof Lateef Akinola Salako (the period 1979 – 1994)**

Prof Salako was born on 5 July 1935 at Otta, Ogun State. Born to humble parents he rose to become one of the most formidable Pharmacologists Nigeria has ever had. He received his education at St. James Anglican School, Otta 1940 – 1947, Methodist Boys' High School, Lagos 1948 – 1953, University of Ibadan Medical School 1954 – 1961, and obtained the MBBS degree of the University of London in 1961. In 1964, he was awarded the MRCP, London, and went on to obtain a Ph.D degree, Sheffield, in 1964. He was appointed Consultant Clinical Pharmacologist, University College Hospital, Ibadan in 1970 and he became a Professor of Pharmacology in 1974. His Ph.D thesis was titled *Studies on the Mechanism of Action of Diuretics 'in vitro'*.<sup>7</sup>



Prof. LA Salako

Prof Salako and colleagues published four significant papers in 1979; one of them reported the pharmacokinetics of pindolol in 12 hypertensive African subjects after a single oral dose of the drug.<sup>8-11</sup> He found that the estimated pharmacokinetic parameters did not differ significantly in Africans from the values that had been observed in other races. In the same group of papers published in 1979, he described the comparative beta-adrenoreceptor-blocking effects and pharmacokinetics of propranolol

and pindolol in hypertensive Africans. Salako and colleagues found that Pindolol diminished systolic blood pressure at rest and after exercise and antagonized exercise-induced tachycardia, but had no effect on resting heart rate and that Propranolol diminished systolic blood pressure predominantly after exercise and reduced both resting and exercise heart rate. Both drugs had no effect on diastolic pressure. In 1971 Salako had written a paper on oral thiazide diuretics in the treatment of hypertension in Nigeria, describing his findings.<sup>12</sup> He would go on to build a very illustrious career in the study of anti-hypertensive medications in Nigerians. During the period spanning 1983 – 1987, Prof Salako published six significant papers on the pharmacokinetics of chloroquine and amodiaquine, the most widely used antimalarials at that time.<sup>13-18</sup> He found that with each route of administration of chloroquine the area under the plasma concentration-time curve was less than that for whole blood, which was in turn less than that for red blood cells. This meant that by whatever route the drug was administered, higher concentrations were reached in red blood cells and whole blood than in plasma, but the concentrations declined at the same rate in the three media thus giving similar half-lives. He also found that the plasma, or whole blood or red blood cell, half-lives varied depending upon whether the drug was given orally, intramuscularly or intravenously. Plasma chloroquine concentrations were determined using High Performance Liquid Chromatography (HPLC) method. Salako found that the plasma half-life of chloroquine was significantly higher in renal insufficiency patients than in controls. This finding suggested that extra caution should be taken when prescribing chloroquine for prolonged use in patients with renal insufficiency. By this time, Prof Salako had become an internationally renowned Pharmacologist.

In 1989, a landmark paper was published by Prof Salako and colleagues describing the Pharmacokinetics of quinine in African children suffering from kwashiorkor.<sup>19</sup> They found that the apparent absorption half-life of quinine was significantly longer in kwashiorkor than in controls. In addition, they discovered that the maximum concentration (C<sub>max</sub>) of quinine was significantly lower in kwashiorkor than in controls. Quinine was eliminated more slowly in children with kwashiorkor with the elimination half-life being significantly longer and the oral clearance significantly less than in controls. It was concluded that kwashiorkor significantly affects the pharmacokinetics of quinine, and that the effect may be due to the pathological changes in the intestine and liver in this condition. In 1992, Salako and Sowunmi reported the disposition of quinine in plasma, red blood cells and saliva after oral and intravenous administration to

healthy adult Africans.<sup>20</sup> They found that the half-lives after the i.v. infusion did not differ from those after oral administration. His studies of antimalarial therapies are now classics; they initiated an era of superlative malaria research that continues to thrive at the department of Pharmacology and Therapeutics, University of Ibadan, to this day. In 1994, Prof Salako and colleagues described an open, non-comparative clinical trial that was carried out in Nigeria and Burkina Faso to investigate the safety and efficacy of the novel antimalarial arteflene in patients with mild malaria.<sup>21</sup> This study showed that a single dose of 25 mg/kg arteflene was found to be an effective and well-tolerated treatment for mild *P. falciparum* malaria. Conducting clinical trials is a major objective of the department of Clinical Pharmacology, University College Hospital, Ibadan. The Department is one of the Legacies of Professor Lateef Akinola Salako. His career spanned through superlative animal and human research on antihypertensives, clinical trials, and malariology.

### Other Notable Early Reports

Aderounmu, who was a collaborator with Professor Salako, made significant contributions to clinical pharmacokinetics. She did work on the pharmacokinetics of chloroquine which on their own were landmark studies.<sup>22,23</sup> Aderounmu reported that different brands of chloroquine in Nigeria, at that time, had similar bioavailability, although with some variations in pharmaceutical properties. Those were days when sub-standard products were rare or even non-existent in Nigeria. Other early workers include Ette and colleagues, who did major work on drug interactions.<sup>24-28</sup> Walker, who was in the same department with Salako, evaluated the disposition of chloroquine after oral and parenteral doses<sup>29</sup>, Essien<sup>30</sup>, Adebayor and colleagues<sup>31-37</sup>, Ehiemua and colleagues<sup>38</sup>, Brown-Awala and colleagues<sup>39</sup>, Atawodi and Maduagwu<sup>40</sup>, Goldzieher<sup>41</sup>, Ogbuokiri<sup>42</sup>, Onyeji<sup>43-48</sup>, and Onyeyeli<sup>49</sup>, and their colleagues worked on different aspects of clinical pharmacokinetics.

This historical review is based on publications listed on PUBMED and many other workers who made significant contributions to clinical pharmacokinetics in the early years of development of the field in Nigeria may not have been listed here. The author acknowledges this limitation. There is a need to continue updating our records of great men and women in the history of scientific research in our nation.

### Evolving Relevance of Clinical Pharmacokinetics

Further growth and development of clinical pharmacokinetics will depend on vast improvements in analytical methods and accompanying technologies.

Advances in engineering will significantly determine the future utility of clinical pharmacokinetics. A miniature, non-invasive, remote, and cheap method of monitoring drug concentrations is still being developed. All advances will be centered on optimizing patient care. Future advances will include developments in the individualization of therapy, *in silico* drug screening and development, advances in sophisticated computer programs with advances in super-computing, defining biological constants that will account for inter-individual variations in drug concentration-time curves, pharmacokinetic-pharmacogenetic inter-phases, development of highly specialized, multidisciplinary, pharmacokinetics laboratories and therapeutic drug monitoring units, and rapid response toxicology units.

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