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 シンポジウム18：病態時の薬物動態試験推進における臨床薬理の役割

2. Opportunities and Challenges of a University-Based Phase I Research Unit

-Experience at the University of Miami-

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Introduction

This symposium presentation was aimed at the discussion of several of the challenges and some of the advantages associated with operating an academically-affiliated phase I CRO. In addition, we describe several of the practical issues we have encountered associated with conducting special populations phase I clinical research studies.

The University of Miami, Division of Clinical Pharmacology has 4 core missions (Figure 1). We operate a phase I clinical research center as a means to generate revenue to support our ongoing academic missions. We have developed special expertise in the design and conduct of special population pharmacokinetic, pharmacodynamic and safety studies including renal impairment, hepatic impairment, postmenopausal hypertension, elderly, and diabetes mellitus (Figure 2). In addition, we support the general medical school research infrastructure by functioning as a core clinical research center and providing the expertise, study design, and research bed resources to support the work of our colleagues.

We also pursue our own original research investigations, investigator-initiated research, and sponsored proof of concept research¹⁻¹²⁾. Our interests involve the effects of drugs on electrolyte homeostasis. We have conducted a number of investigations into the effects of drugs on potassium excretion by the kidney and the effects of antihypertensives on sodium sensitivity. Finally, we serve as an educational component of the clinical-translational program.

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Overview of Phase I Clinical Research Operations

The University of Miami, Division of Clinical Pharmacology has been conducting Phase I, II and III clinical research for pharmaceutical and biotech companies for

Fig. 1

Figure 2. The University of Miami experience

- Renal impairment studies (56 total studies)
- Hepatic impairment studies (58 total studies)
- Elderly PK/PD
- Postmenopausal hypertension
- Healthy volunteer phase I
- Proof of concept studies
 - Example: Effects of drug X on sodium handling
 - Example: Effects of drug Y on potassium excretion
 - Example: Mechanism of edema for drug Z
- Original projects

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Fig. 2

more than 20 years. Despite being university-based, we have developed an efficient mode of operation compatible with the expectations and time concerns of modern pharmaceutical companies. Our combined phase I inpatient and outpatient center is located directly on the medical campus of the University of Miami School of Medicine.

Recruitment of Special Populations

The University of Miami Medical School complex has three large teaching hospitals and their numerous associated specialty clinics: Jackson Memorial Hospital (1200 beds), the Miami VA Medical Center (800 beds) and the University of Miami Hospital (700 beds). As one of the largest medical centers in the United States, our phase I unit draws from a huge patient population base and a large number of specialty clinics. I interact closely with faculty members in various departments within the School of Medicine and our center can therefore accomplish enrollment for protocols requiring special populations that would otherwise be difficult to recruit.

Because of the enormous patient database associated with these teaching hospitals, our phase I unit can successfully conduct pharmacokinetic and pharmacodynamic studies in special populations such as renal impairment, hepatic impairment, postmenopausal, elderly and other special disease populations. We conduct 4-5 studies in renal impairment and 4-5 studies in hepatic impairment per year. We have a large active database of renal and hepatic subjects who have successfully completed studies with us in the past. I have been PI of more than 150 clinical research studies and have been director of this phase I unit for 11 years.

IRB Approval and Contracts

A significant concern among those responsible for placing phase I studies is the lengthy and often frustrating process of IRB review and approval associated with a university-based research site. Project timelines can be unnecessarily delayed if the IRB is not specially streamlined for phase I studies. In response to this concern we have developed a special fast track process. The turnaround time on IRB approvals is approximately 2 weeks and our contracts and agreement process can be accomplished in parallel. This cooperation from the administration of the university has been critical in allowing us to compete successfully with private CRO who utilize larger and efficient IRBs. Thus we have successfully eliminated two of the major barriers to the success of an academic-based CRO.

Advantages of an Academic CRO

There can be significant opportunities for patient recruitment in a large academic center. The University of Miami has a large Center for Liver Disease under the direction of Eugene Schiff, MD. The center has an active transplantation program and a large database of patients with mild, moderate, and severe liver impairment. We have extensive experience in conducting studies in patients with hepatic cirrhosis and have conducted approximately 58 such studies over the past 12 years. We are often asked to review draft protocols or to help develop original protocols. The patients for the studies are recruited rapidly from our own patient base of 50-60 subjects. Because most hepatic impairment protocols require in the neighborhood of 16-24 subjects and their healthy controls, we are able to enroll most studies within a brief time frame.

Hepatic Impairment Studies

There are certain challenges associated with studies of pharmacokinetics in hepatic impairment. For example, the Child-Pugh classification of liver disease which is used to stratify patients can often be confusing for the CRA writing his or her first liver impairment protocol. The Child-Pugh categorization takes into account the synthetic function (albumin, prothrombin time), the excretory function (bilirubin), and the detoxification function (encephalopathy) of the liver. In an individual patient these functions are often not impaired to equal degrees. For example, a patient with mild encephalopathy (Figure 3) may have entirely normal prothrombin time and bilirubin. Alternatively, the albumin and prothrombin time (some use INR) may be abnormal with a normal or perhaps mildly increased bilirubin.

Subjects often have concomitant illness and conditions associated with the underlying cause of the liver disease. For example, a patient may develop an abrupt worsening of encephalopathy associated with protein intake of gastrointestinal bleeding. We have seen cases of spontaneous peritonitis develop in study participants resulting in the clinical picture of an acute abdominal crisis. Significant liver disease can result in hypoalbuminemia and bleeding disorders. Finally, there are a number of common medications that patients with liver impairment receive including lactulose, neomycin, beta-blockers. In addition, patients with liver disease can have common and unrelated illnesses such as diabetes mellitus and hypertension. We have also found that a significant number of hepatic subjects are tobacco users.

Studies of Pharmacokinetics in Renal Impairment

Our medical complex has several active outpatient renal

Figure 3. Challenges in conducting hepatic studies

- Child-Pugh classification
- Encephalopathy
- Spontaneous peritonitis
- Bleeding disorders
- GI hemorrhage
- Hypoalbuminemia - decreased effective intravascular volume
- Concomitant common medical conditions
 - Diabetes mellitus
 - Hypertension

Fig. 3

centers and a large ambulatory population of patients with renal impairment. There are a number of challenges with the conduct of renal impairment studies over the past 12 years (Figure 4). There are 20 million patients in the US with Stage 3 kidney disease (estimated GFR < 60 mL/min). This group has a 10-fold greater risk of cardiovascular disease and a 3-fold greater risk of sudden death. In addition, there are 292,000 in the US with end stage renal disease requiring renal replacement therapy¹³⁻¹⁸⁾. Despite these large numbers, renal impairment phase I studies are notoriously difficult to conduct. For example, in the US, there are only a handful of centers that can successfully conduct renal impairment studies.

A number of commonly encountered concomitant medical conditions can make renal impairment studies difficult to conduct (Figure 4). Renal impairment is associated with a very high rate of cardiovascular disease and this rate increases as the GFR declines. Underlying cardiovascular disease is prevalent even in patients who have “no history” of cardiovascular disease. Diabetes mellitus is the leading cause of kidney disease in the US and is increasing in prevalence at an alarming rate. In addition, there are several co-morbidities common to diabetes mellitus that can complicate a PK-safety study and lead to adverse events. In writing a renal impairment study protocol it is essential to consider some of the key concerns related to the diabetic patient. For example, prolonged fasting should be avoided and insulin and oral hypoglycemic agents allowed in the protocol. In addition, because of the association of obesity with type II diabetes, wider BMI ranges should be allowed.

Hypertension associated with renal impairment is often refractory and poorly controlled despite multiple antihypertensive agents. In addition, the hypertension may be quite sensitive to dietary sodium making control difficult.

Figure 4. Co-morbidities in Chronic Kidney Disease

- Cardiovascular Disease
- Diabetes Mellitus
 - Retinopathy
 - Neuropathy
 - Peripheral vasculopathy
 - Obesity
- Hypertension (refractory)
- Renal cystic disease
- Metabolic bone disease
- Peptic ulcer disease
- Platelet dysfunction
- Acute electrolyte disorders

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Fig. 4

It is common to see wide fluctuations in blood pressure in patients with CKD, especially hemodialysis subjects. There are some common lab abnormalities encountered in renal patients. The metabolic bone disease associated with CKD may lead to an elevation of the alkaline phosphatase bone fraction, giving the impression of abnormal liver function. Unless one is aware of this, it may lead to unnecessary screen failures and delayed study completion.

As a result of the numerous concomitant morbidities associated with CKD, there are a number of medications that are often encountered that can complicate the conduct of a PK study. Renal patients often require several antihypertensives. Calcium channel blockers are frequently utilized in this population. Diltiazem and verapamil are potent inhibitors of CYP3A4 whereas amlodipine and nifedipine inhibit CYP3A4 only minimally. A protocol that excludes all calcium antagonists will also exclude the commonly utilized amlodipine and nifedipine and will result in the unnecessary exclusion of otherwise qualified subjects.

Diuretics are a cornerstone of the management of the sodium sensitive hypertension associated with CKD, but can lead to electrolyte abnormalities including hypokalemia, hyponatremia, and hypercalcemia. How to handle these routine electrolyte disorders without unnecessarily withdrawing study subjects is a key protocol design issue.

Because of the high prevalence of cardiovascular disease among the renal population, aspirin and antiplatelet agents frequently encountered. In addition, many patients will receive anti-cholesterol agents, most commonly HMG Co reductase inhibitors. Iron prescribed for anemia and binding agents prescribed for metabolic bone disease can potentially interfere with the absorption of study drug.

In general, the challenges presented by a renal impairment study will require some modifications to the

standard healthy volunteer study. Renal patients will require wider blood pressure limits for inclusion/exclusion criteria that will allow for the difficulty in controlling blood pressure and the fluctuations related to salt-sensitivity. Because obesity is common in the CKD population, the BMI limits should be appropriately expanded. Concomitant conditions and the medications used to treat these conditions should be proactively considered and a provision for substitution medications made. For example, allowing the substitution of a calcium antagonist with minimal CYP3A4 inhibiting characteristics such as amlodipine for a strong CYP inhibitor such as diltiazem can help with study recruitment and timelines. Finally, we have found that a method of GFR estimation that does not require timed urine collections is superior to the standard 24-hour creatinine clearance. There are several caveats that one must consider in deciding upon a GFR estimation method.

Summary

We have discussed some of the advantages and challenges of operating an academic phase I CRO and some of the challenges associated with conducting special population phase I research in an academic environment. In regards to a large academic center, the recruitment advantages, the availability of a wide variety of consultants, and the expertise in conducting special populations studies have proved advantageous for our operation. In addition, a streamlined IRB process and contracts have allowed for a shorter start-up time than the typical university-based research operation. On the other hand, special populations research is always challenging due to the nature of the special populations, recruitment challenges, concomitant illnesses, complications, and a variety of commonly encountered concomitant medications.

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