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Commentary

Imaging Can Be Much More Than Pretty Pictures

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The study of human pathophysiology requires assessment of the status of selected human organs and tissues, as well as of any changes induced by various interventions. The methods used in such studies go under the general name of **imaging** techniques, and are, generally, performed as noninvasively as possible so that they do not alter or perturb the organs, tissues or functions that are to be measured.

Although the term "imaging" conjures a pictorial representation of human anatomy, its significance goes well beyond that, and encompasses a range of measurements in living systems. I wish to propose here a new classification of imaging methods into two groups: those where the measurements of anatomic features are central, and those centered on measurements of specific products. Each group has a static and a dynamic modality. Fig. 1 illustrates the four imaging methods.

It must be stressed that some of these terms have been used before. Indeed, much of Nuclear Medicine is based on its ability to provide physiological information, and the terms "physiological imaging" and "anatomical imaging" have been used widely before (1). The notion of localizing specific chemical entities to anatomical spaces has been described as "spectroscopic imaging" or "chemical shift imaging" (2). What is novel here is that by recognizing a new imaging modality ("pharmacokinetic imaging"), the symmetry and the relationship between all these imaging modalities can now be visualized more clearly.

Anatomical Imaging includes all the most common methods used in Radiology, with images being acquired in either 2-dimensional modes (X-ray, planar nuclear medicine, ultrasound) or in a 3-dimensional reconstruction (CT, MRI, nuclear medicine SPECT and PET). While each of these methods has advantages and limitations, they do provide very reliable information of the anatomical features of the human body, and of the presence of any eventual abnormalities.

When, using these same techniques, we add the dimension of **time**—e.g., we measure the **changes** that occur in an anatomical organ or tissue site, then such methods can be labelled as **functional imaging** techniques. Examples include the measure of cardiac function by nuclear medicine imaging, of angiography by MRI, etc.

The above methods focus on anatomic aspects of the human body. Some of these same methods can also be used for measuring specific chemical entities. Thus, when we measure a specific chemical compound (or a family of chemical compounds) in a given anatomic space, then we perform **chemical imaging.** Nuclear medicine techniques, which image the anatomical distribution of gamma-emitters, are a prime example. If we now add the dimension of **time** to chemical imaging, then we perform what can be labelled as **pharmacokinetic imaging**—the measure of the rate of change of a chemical compound in a clearly defined anatomic space.

What is the potential significance of such methods for drug studies? The anatomically based methods are used to monitor the response of a patient to specific drugs, by determining the changes occurring in anatomic features—has a lung cleared when a given drug has been used, has the size of a tumor changed?. They can also measure functional changes—has the function of the cardiac muscle improved by drug treatment?; has there been a change in the rate of utilization of glucose in brain lesions?

Noninvasive imaging methods can do much more, however, than monitor changes in the patient's anatomical features: they can provide a unique and hitherto untapped window for monitoring what happens to a specific drug that is being administered to a living system. The following is a list (certainly not inclusive) of some studies that are possible now using both spectroscopic and pharmacokinetic imaging approaches.

- What is the **biodistribution** of that drug?
- How much of the drug has been deposited at its intended target site—e.g., what is the patient's **exposure** to that drug?
- What are the **chemical** changes (metabolism) that befall to that drug, where do its biotransformations occur and at what rate will that drug be converted into its active—or its inactive—metabolites?
- What is the **pharmacokinetics** of that drug at its target site—as opposed to blood based pharmacokinetics, which can only infer (based on various assumptions) what may be happening at organ and tissue sites?
- We can also look at physiological products present at the target site. For example, how does the drug administered alter the metabolism of a given chemical entity at that site?
- What is the relationship between the **pharmacokinetics** of this drug, and its **pharmacodynamics**?

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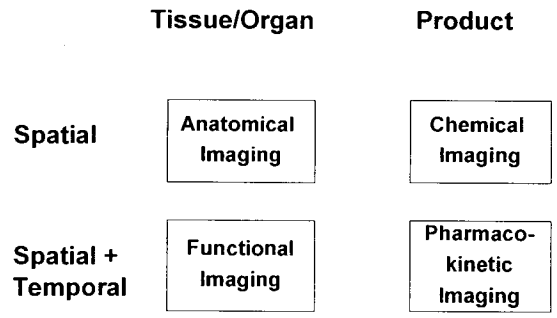

Fig. 1. Relation between the various imaging methods.

Let me conclude by illustrating the potential of these noninvasive **pharmacokinetic imaging** methods with two types of studies performed in our laboratory, both of which allow the measurement of specific products, *in vivo,* and noninvasively: nuclear measurements of drugs that have been radiolabeled with a gamma emitter, and nuclear magnetic resonance spectroscopy (NMRS) of drugs where one or more of its constituent atoms has NMR-detectable characteristics. Both of these two methods have advantages as well as limitations. While NMRS has exquisite chemical resolution, it has extremely poor sensitivity: the spectral characteristics of a compound identify that molecule, but concentrations near the milli-molar range are required. The detection of gamma emitters has extremely high sensitivity, but is totally devoid of chemical resolution: one nuclear decomposition represents a single atomic event, and the information lumps together all compounds labelled with the same radioactive atom.

A typical noninvasive dynamic measurement using NMRS is illustrated in Fig. 2, in a patient who had received 5-fluorouracil (5-FU) for the treatment of basal cell carcinoma. The chemical shift of the NMR spectrum identified the product whose kinetic behavior is being measured as that of free 5-FU, while the rate of change allowed an estimation of its $t_{1/2}$, a parameter we have documented as being highly

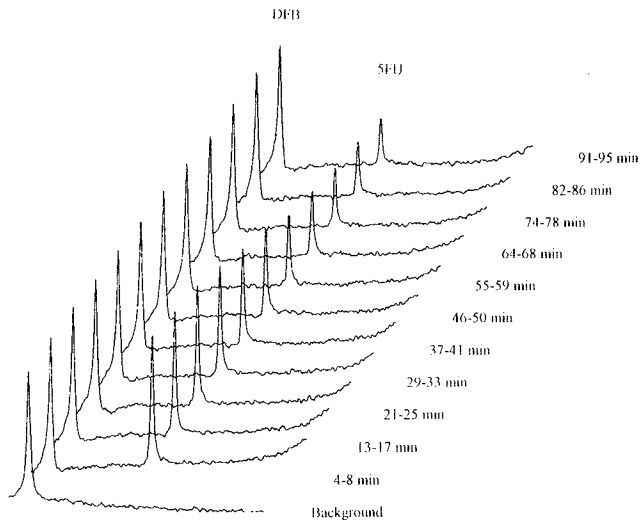

Fig. 2. Stacked plot of the ^{19}F-NMR spectra from patient SV91 following the intralesional administrating of 30 mg of 5-Fluorouracil (5FU) (Matrix Pharmaceutical, 5FU/Gel) to basal cell carcinoma. The external reference standard is 1,2-difluorobenzene.

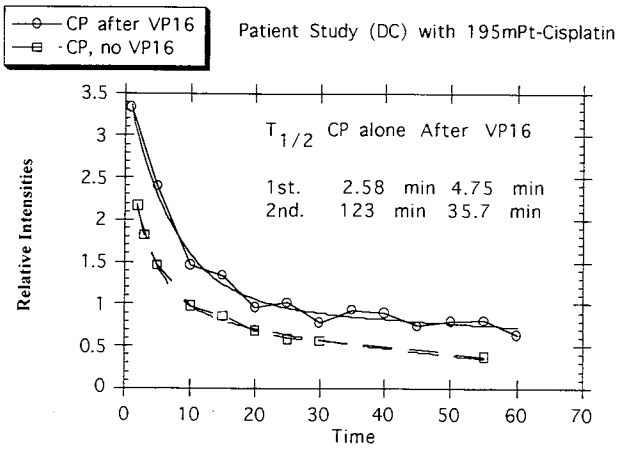

Fig. 3. Comparative kinetics of ^{195m}Pt in a brain tumor of a patient (DC), following administration of ^{195m}Pt-cisplatin either alone or after a modulating dose of VP16 (etoposide).

predictive of responsiveness to treatment (3). Other pharmacokinetic parameters detailing drug behavior at the tissue site can be estimated from such noninvasive **pharmacokinetic imaging** measurements.

The plot in Fig. 3 illustrates the comparative time course of ^{195m}Pt, following administration of ^{195m}Pt-cisplatin, in a patient with a high grade glioma, where significant **kinetic** differences of the degree and the rate of drug targeting could be observed when VP-16 was used as a modulator (4).

We believe that these **noninvasive imaging** methods, and especially, **pharmacokinetic imaging,** can open up entirely new vistas and approaches to drug studies: they allow the development of novel strategies for optimizing drug effectiveness, for performing organ-based pharmacokinetic/pharmacodynamic measurements, and in the rational development and testing of new drugs.

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