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# Microdialysis Versus Other Techniques for the Clinical Assessment of In Vivo Tissue Drug Distribution

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## ABSTRACT

Quantification of target site pharmacokinetics (PK) is crucial for drug discovery and development. Clinical microdialysis (MD) has increasingly been employed for the description of drug distribution and receptor phase PK of the unbound fraction of various analytes. Costs for MD experiments are comparably low and given suitable analytics, target tissue PK of virtually any drug molecule can be quantified. The major limitation of MD stems from the fact that organs such as brain, lung or liver are not readily accessible without surgery. Recently, non-invasive imaging techniques, i.e. positron emission tomography (PET) or magnetic resonance spectroscopy (MRS), have become available for in vivo drug distribution assessment and allow for drug concentration measurements in practically every human organ. Spatial resolution of MRS imaging, however, is low and although PET enables monitoring of regional drug concentration differences with a spatial resolution of a few millimetres, discrimination between bound and unbound drug or parent compound and metabolite is difficult. Radiotracer development is furthermore time and labour intensive and requires special expertise and radiation exposure and costs originating from running a PET facility cannot be neglected. The recent complementary use of MD and imaging has permitted to exploit individual strengths of these diverse techniques. In conclusion, MD and imaging techniques have provided drug distribution data that have so far not been available. Used alone or in combination, these methods may potentially play an important role in future drug research and development with the potential to serve as translational tools for clinical decision making.

**KEYWORDS:** microdialysis, drug distribution, positron emission tomography (PET), magnetic resonance spectroscopy (MRS), in vivo

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## INTRODUCTION

Currently, in the light of rapid advances in the genetic field, the concept of personalized medicine is receiving much attention.[1] The idea of dose individualization, however, is not new. The aim of giving the right dose of a drug to the right patient in order to achieve a maximum therapeutic effect with a minimum of drug-related side effects has been a component of algorithms for therapeutic decision making for centuries. Promoting idea and practice of dose individualization has become a prime mission of the discipline of clinical pharmacology and is based on and supported by increasing knowledge about the variety of factors that determine individual patient variability in drug response.

One of the factors known to contribute to drug response variability is tissue drug distribution. Drug effects are mediated by interactions with different target structures such as enzymes, drug transporters, or receptor proteins, which are usually located in defined compartments of the body and not within the plasma compartment. Thus, the dose-effect relationship is dependent upon distribution of the active drug fraction to the binding sites. This discovery led to the concept of the target site concentration as a direct link to therapeutic drug effects[2] and direct target tissue concentration measurements as a means of optimizing individual drug therapy. Although it has been recognized that most drugs do not distribute uniformly in the body but rather attain varying concentrations in different tissues[3] and that tissue concentrations are more predictive of clinical outcome than plasma concentrations in some cases,[4,5] the assessment of drug distribution and target site pharmacokinetics (PK) has long been treated as a "forgotten relative" in clinical pharmacokinetics.[6] The main reason has been a lack of appropriate methodology providing in vivo access to the target sites, and consequently PK research was long restricted to drug concentration measurements from biological specimens that are relatively easy to obtain, such as tissue biopsies, urine, saliva, or skin blister fluid or to indirect modeling of tissue concentrations from plasma concentration curves.

Within the last years, several novel techniques for the assessment of drug distribution and target tissue PK in humans have become available, including in vivo microdialysis (MD),[7-9] magnetic resonance spectroscopy (MRS),[5,10-12] and positron

emission tomography (PET).[11-13] The rapid technical advances in medical imaging have promoted an increasing number of publications on drug PK relying on imaging techniques ("pharmacokinetic imaging").[14] Results from clinical studies employing MD and/or imaging techniques have furthermore underlined the importance of the previously neglected drug distribution process to the target site as a crucial determinant for clinical outcomes, and that this process contributes more to variability in the dose-effect relationship than variability in plasma PK.[4,5] With the increased use of imaging technologies in drug development, imaging data are increasingly being used in product registration dossiers for submission to regulatory authorities. The Food and Drug Administration (FDA) and Committee for Proprietary Medicinal Products (CPMP) documents further emphasize the value and importance of human tissue drug concentration data and support the use of clinical MD to obtain this information.[15,16]

The present review aims at providing a short comparative description of MD and other techniques, in particular imaging techniques, for the assessment of in vivo tissue drug distribution, addressing advantages and limitations as well as potential combinations.

## MICRODIALYSIS

MD is a semi-invasive, focal sampling method, based on the use of probes with a semipermeable membrane at the probe tip. The MD probe, which is constantly perfused with a physiological solution at a low flow rate of 1 to 10 μL/min is implanted into the tissue of interest, and substances in the interstitial space fluid pass the membrane by passive diffusion along their concentration gradient resulting in a certain concentration in the perfusion medium. This dialysate is collected at timed intervals and is subjected ex vivo to different types of chemical analyses, which can be performed either in an off-line or on-line fashion. Depending on the molecular cut-off of the membrane, large molecules such as proteins are usually excluded from the dialysate, which enables analysis without time-consuming sample preparation or sample storage without the immediate fear of enzymatic degradation. Owing to small sample volumes, which are usually in the microliter range in human studies, there is no substantial biological fluid loss. Sample analysis, however, requires highly sensitive methods such as liquid chromatography-tandem mass spectrometry (LC-MS-MS) to deal with the low concentrations in a rather small sample volume. In most of the cases, MD is performed under non-equilibrium conditions, and dialysate concentrations represent only a fraction of actual concentrations in the medium surrounding the MD probe. To obtain and quantify interstitial space fluid concentrations from dialysate concentrations, MD probes need to be calibrated. Provided proper in vivo calibration procedures, intra-individual variation for interstitial space fluid measurements was shown to range between 10% and 20% depending on the analyte.[17] In contrast to other traditionally applied methods for tissue concentration measurements, MD provides selective access to the unbound and thus pharmacologically active drug fraction in the interstitial space fluid of tissues, the true target site for drugs such as most antimicrobial agents, tumor chemotherapeutics, or substances that act by binding to cell surface receptors.

In clinical research, MD is currently employed to address various issues in different clinical fields, such as monitoring of secondary ischemia in neurointensive care[18] or glucose monitoring for long-term metabolic control in patients with diabetes mellitus.[19] Further areas of research comprise studies on the local physiology of peripheral tissues[20] or the local administration of drugs by MD without inducing systemic side effects and the simultaneous measurement of the corresponding tissue response.[21,22] In clinical pharmacology, research focuses on the use of MD to measure target site concentrations of antibiotics[23] or anticancer drugs[24] in different tissues and organs and to subsequently relate target site PK to pharmacodynamics.[25] Equally challenging is the characterization of skin penetration of analytes from transdermal therapeutic systems.[26] In contrast to other often technically demanding and expensive methods such as imaging techniques, MD can be readily employed for clinical studies in almost any research center at a reasonable price (Table 1). Drawbacks of the technique stem from the semi-invasive nature of the technique. Consequently, most human studies have been performed in easily accessible tissues such as skeletal muscle, subcutaneous adipose tissue, skin, tendons,[27] superficially located tumors,[28-30] or blood.[31] Combined with surgical procedures, however, almost every tissue within the human body is in reach for MD probe implantation as demonstrated by studies in brain,[32,33] lung,[34,35] bone,[36] heart,[37] liver,[38] or the peritoneal cavity.[39] For the latter 2 applications, special probes for the use in humans have become available recently. Recent review articles offer an in-depth view on methodological aspects and clinical applications of MD.[8,9,12,20,40-42]

## MICRODIALYSIS COMPARED WITH TRADITIONAL TECHNIQUES FOR TISSUE CONCENTRATION MEASUREMENTS

Traditionally, tissue biopsies, saliva sampling, or skin blister fluid measurements have been used to measure drug tissue concentrations, as they are relatively simple to perform. Unlike MD, which yields concentrations measurements from the interstitial space fluid of tissues, concentration measurements from biopsy specimens yield information on total drug concentrations from the admixture of various

**Table 1.** Comparative Characteristics of Techniques for the Clinical Assessment of Tissue Drug Distribution in Humans*

| | | Imaging Methods | | "Traditional Methods" | | |
|---|---|---|---|---|---|---|
| | **Microdialysis** | **PET** | **MRS** | **Tissue Biopsy** | **Skin Blister Fluid Sampling** | **Saliva Sampling** |
| Matrix sampled/ measured | Extracellular fluid | Total tissue | Total tissue | Total tissue | Blister fluid | Saliva |
| Invasiveness | Semi-invasive | Noninvasive (but radioactive exposure) | Noninvasive | Invasive | Semi-invasive | Noninvasive |
| Direct measurement of unbound drug concentrations | Yes | No (free and bound concentrations) | Yes | No (free, bound, vascular concentrations) | No | No |
| Measurements at multiple sites | Yes | Yes | Yes | No | No | No |
| Continuous monitoring | Yes | Yes (duration restricted by physical half-life of employed radioisotope) | Yes | No | No | Yes |
| Technical complexity | Low | High | High | Low | Low | Low |
| Costs | Low | High | High | Low | Low | Low |
| Major disadvantages affecting the use in clinical drug distribution studies | Time consuming calibration; mostly restricted to low molecular weight substances | Limited number of drugs eligible for labeling; inclusion of metabolite signal; highly specialized center required | Low sensitivity; limited number of eligible drugs | Invasiveness; hybrid tissue concentration owing to mixture of different compartments | Difficult to standardize; contains proteins; limited number of time points | Conflicting results regarding free drug concentrations when compared with microdialysis |

*PET indicates positron emission tomography; and MRS, magnetic resonance spectroscopy.

compartmental fluids during specimen processing (Table 1). The resulting hybrid tissue drug concentration, however, is difficult to interpret.[3] For most antibiotics, for example, the true target site is the interstitial space fluid. Consequently, if total tissue drug concentrations are measured, effective concentrations of drugs that equilibrate exclusively with the extracellular space, such as β-lactam antibiotics, may be underestimated.[43] On the other hand, effect site concentrations of intracellularly accumulating drugs, such as quinolone antibiotics or macrolides, might be overestimated.[43] From a practical perspective, taking biopsies has obvious ethical limitations and usually yields only a limited number of time points for analysis.

As a technique for assessing interstitial concentrations in the skin, the induction of skin blisters by applying negative pressure or chemical irritants to intact skin with subsequent analysis of the blister fluid has been applied for several decades.[44] Skin blister techniques rely on the separation of the epidermis from the dermis and the subsequent formation of a fluid-filled compartment, which is believed to serve as a surrogate for the interstitial space. Studies comparing MD and skin blister techniques, however, have yielded controversial results. In case of chemically induced skin blisters, discrepancies between drug concentrations in blister fluid and interstitial space fluid might arise because blister fluid is an inflammatory exudate with proteins and chemokines, which cannot be compared with the interstitial space fluid sampled by MD.[45] Furthermore, drug concentrations in blister fluid might vary with blister size and the surface-to-volume ratio.[46] For ciprofloxacin and moxifloxacin, for example, preferential penetration into skin blister fluid has been described, whereas an almost-complete equilibration of the free unbound antibiotic plasma fraction with the interstitial space fluid was observed using MD.[47,48] Compared with MD, skin blister sampling is also not feasible for continuously monitoring drug PK, as only a limited number of time points can be obtained (Table 1). Induction of blisters might furthermore cause discomfort for several days at the

area of blistering, and hyperpigmentation might occur, which has been reported to persist for up to 6 months.[45]

Drug concentration measurements in saliva have also been advocated as simple, noninvasive surrogate for drug concentrations in peripheral compartments. Studies comparing saliva sampling and MD, however, could not recommend saliva sampling for the determination of interstitial drug concentrations of 2 model drugs, paracetamol[49] and theophylline.[50] In both studies, MD measurements closely mirrored free plasma concentrations, whereas saliva data overestimated the corresponding concentrations attained in plasma. The authors concluded that MD represents a reliable technique for the measurement of unbound peripheral compartment concentrations and is superior to saliva measurements.

## Imaging Techniques

In the last 20 years, imaging techniques have evolved as powerful tools for the noninvasive study of drug distribution in vivo as well as for studying drug effects at their target sites. Imaging techniques that lend themselves to the study of drug distribution in humans comprise magnetic resonance spectroscopy (MRS)[5,10,11,51] and positron emission tomography (PET).[13,14,52,53] Although these techniques were initially introduced to clinical medicine for diagnostic purposes and for the study of tissue metabolism and blood flow,[54] they also opened a unique opportunity for PK research by providing a means for noninvasive measurement of drug distribution from the plasma compartment to anatomically defined regions and for the visualization of the entire pattern of drug distribution in given organs.[55,56]

## Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy

Magnetic resonance imaging (MRI) uses radio-frequency pulses and magnetic fields to obtain signals from changes in nuclear magnetic moments. A technique based on the same principle as MRI, but providing a greater degree of molecular characterization is MRS, in which spectroscopic profiles of the chemical constituents within a sample are obtained.[57] MRS measurements can be performed serially, thus giving the possibility of PK analysis with a temporal resolution in the order of minutes. Of importance, MRS is capable of resolving different chemical species including metabolites owing to different chemical shifts of the resonance signals. This poses a considerable advantage over nuclear imaging methods such as PET, which record nuclear decay events irrespective of the chemical surrounding of the decaying atom and therefore lump together all compounds labeled with the same radioactive atom. A main limitation of all nuclear MR-based methods is their inherent low sensitivity, which restricts the in vivo applicability mainly to molecules that are present in large concentrations in the human body. MRI has proven to be particularly feasible for fluorinated drugs (Table 1), since $^{19}F$ is one of the lead isotopes for nuclear MRS, and several studies have been published describing brain PK of fluorinated psychiatric medications,[58] tumor uptake of anticancer chemotherapeutics, or bio-distribution and target tissue PK of fluorinated antibiotics.[51,59]

## Positron Emission Tomography

PET is a nuclear imaging technique based on the use of molecules labeled with positron-emitting radioisotopes. The emitted positrons pass through tissue and are ultimately annihilated when combined with an electron, resulting in two 511 keV photons emitted in opposite directions. Detectors are arranged in a ring around the tissue of interest, and only triggering events that arrive near-simultaneously at diametrically opposite detectors are recorded ("coincidence detection"). The resulting PET images might yield 3-dimensional information on tissue distribution of the positron-emitting molecules with a spatial resolution of 1 to 5 mm and a maximum temporal resolution of ~30 seconds. The most commonly employed PET radionuclides are oxygen-15 ($^{15}O$), nitrogen-13 ($^{13}N$), carbon-11 ($^{11}C$), and fluorine-18 ($^{18}F$). Owing to its comparably long half-life, $^{18}F$ is the most attractive PET radioisotope, since it allows for imaging durations of up to 10 hours. A considerable drawback, however, is that relatively few drug molecules contain fluorine in their native structure; consequently, despite the rather short $t_{1/2}$ of $^{11}C$ (20.4 minutes), the majority of PET/PK experiments have relied on $^{11}C$-labeled tracer molecules. PET has been used to study tissue distribution of radiolabeled antibiotics, antifungals, and inhaled drugs in patients and volunteers.[13,56,60-62] Recently, we have employed PET to describe tissue pharmacokinetics of $^{18}F$-labeled ciprofloxacin in several tissues over several hours in healthy volunteers[56] and patients with foot infections,[63] and we have compared intracerebral uptake of $^{11}C$-labled verapamil in volunteers differing in genotypes for the drug efflux transporter gene *ABCB1*.[64] Furthermore, PET has proven to be a valuable noninvasive means for characterizing established and novel anticancer agents.[65] Using PET imaging, it was demonstrated that radioactivity uptake was correlated with response to chemotherapy.[66] Using PET imaging, the postulated mechanisms of a newer antineoplastic agent, temozolomide, were recently confirmed in vivo in glioma patients.[67]

Altogether, studies using imaging techniques such as PET and MRS provided evidence that tissue distribution contributes more to total variability in the dose-effect relationship than the combination of factors determining plasma PK.

PET and MRS were also shown to support the definition of optimal dosing schedules in phase 1 and 2 studies and in the design of phase 3 studies.[52] There are important limitations of these techniques because only drugs that lend themselves to radiolabeling or the induction of an appropriate magnetic response may be studied (Table 1). In addition, the signal produced by imaging techniques is not necessarily a measure of the intact drug concentration, and imaging techniques are not able to provide information about specific tissue compartments, such as the interstitial space fluid. PET studies are furthermore bound to specialized centers, with on-site access to a cyclotron, radiochemistry, and a PET camera, which substantially contributes to the high cost of PET studies.

## Combination of Microdialysis and Imaging Techniques

So far, only a few preclinical studies have been published combining MD and imaging techniques, but none of these studies has addressed purely pharmacokinetic issues. Even fewer MD/PET combinations have been published in the clinical setting, most of them in the neurosurgical field to study alterations of brain metabolism as a consequence of brain trauma or surgery.[68,69] MD was introduced as an intracerebral sampling method for clinical neurosurgery in 1990[70] and has since been embraced as a safe and effective monitoring technique to measure the neurochemistry of acute brain injury[71] and epilepsy.[72] Although data from brain MD studies strongly suggest that changes in local markers of brain metabolism might precede the onset of secondary neurological deterioration,[70] the initial enthusiasm for brain MD has subsided over the years because of concerns about the amount of tissue sampled, quantification issues, and the notion that brain MD data contribute only a single, albeit vital, component to the understanding of the neurochemical picture.[70] MD is still mainly used as a clinical research tool in neurosurgery, and its use to influence clinical therapeutic decision making has been restricted to only a few institutions worldwide. Still, brain MD is one of few methods for neurochemical measurements in the interstitial compartment of the human brain and has become a valuable translational research tool, providing new and important insights into the neurochemistry of acute human brain injury. Isolated interpretation of biomarkers derived from brain MD experiments, however, should be done cautiously and might require additional validation, particularly in clinical studies in which experimental conditions cannot be easily standardized. Therefore, the simultaneous use of complementary methods such as MRI (eg, to get an additional estimate of intracellular changes or arterial-venous differences) and PET (to compare metabolic rates) might be crucial for biomarker interpretation.[70] Promising MD applications, as yet less explored in combination with imaging techniques, include local neurochemical provocations, drug penetration to the brain, and a technique to obtain surrogate end point(s) in neuropharmacological studies.

A recent study by Vespa et al combined MD and PET with the aim to determine the occurrence of a metabolic crisis after brain injury by examining a representative region of brain tissue remote from the primary injury site.[73] In this region they measured the metabolic state of the tissue by PET and MD and furthermore validated the usefulness of MD as an indicator of ischemia in traumatic brain injury. The main findings of the study were that the injured brain had persistent impairments in metabolism that could be detected by brain MD. The lactate/pyruvate ratio, an MD marker that has been proposed to be a reliable marker of ischemia in previous MD studies,[18] reflected impaired oxidative metabolism. However, the ratio was not specific for brain ischemia in the investigated region as shown by simultaneous PET measurements, suggesting that energy perturbation unrelated to ischemia may contribute to secondary brain damage in traumatic brain injury.

A series of studies has employed the MD/PET combination for regional metabolic imaging[74-76] or to predict malignant edema progression in patients with brain infarctions.[77] Although all MD neuromonitoring parameters were significantly altered at the time of manifest malignant edema causing a midline shift, only PET could predict this unfavorable clinical course by revealing larger volumes of ischemic core and irreversible neuronal damage during the first 24 hours. The authors concluded that in contrast to PET, MD monitoring failed to predict a fatal outcome in time for successful therapeutic intervention. In a later study, however, the same group studied stroke patients, used other MD biomarkers, and came to the opposite conclusion.[74] The results from these 2 studies underline the importance of the combined use of MD and imaging to accurately interpret the obtained results and to translate the data into clinically useful information.

Apart from the neurological field, 2 recent human studies have used the MD/PET combination to measure the lumped constant, an experimentally-derived correction factor that accounts for the differences in transport and phosphorylation between 2-[$^{18}$F]fluoro-2-deoxy-D-glucose ([$^{18}$F]FDG), a widely used PET tracer for glucose utilization, and its endogenous counterpart glucose.[78,79] Regional [$^{18}$F] FDG uptake was determined in skeletal muscle or adipose tissue by PET, whereas MD was used to monitor local interstitial glucose concentrations. Furthermore, regional tissue blood flow was determined by [$^{15}$O]$H_2O$/PET, and regional glucose uptake was calculated.

Finally, a recent study by Langer et al[80] combined MD and PET to assess intracellular drug pharmacokinetics in vivo. Both techniques have been used to study tissue drug

delivery and target site pharmacokinetics. PET, however, yields a combined signal comprising the intracellular, the extracellular, and the intravascular fraction of a radiolabeled drug and its metabolites in a given volume of tissue, whereas MD describes unbound extracellular drug concentrations. As for several drugs, such as certain anti-infective and anticancer agents, the site of drug action is not the biophase surrounding the cells but rather an intracellular compartment, and knowledge of intracellular rather than extracellular or total drug concentrations is relevant in many cases. Fluorine-18-labeled ciprofloxacin ([$^{18}$F]ciprofloxacin)[81] was used as a model compound to perform simultaneous PET imaging and MD in healthy volunteers to describe intracellular drug pharmacokinetics in human muscle tissue for several hours. A 3-compartment pharmacokinetic model was fitted to the tissue concentration-time profiles of ciprofloxacin measured by PET in order to estimate the rate constants of ciprofloxacin uptake and transport. The predicted extracellular concentration-time profiles from the compartmental modeling were in good agreement with the measured MD data, and the results were in accordance with previous in vitro data describing cellular ciprofloxacin uptake and retention. The setting of this study is unique in the sense that it constitutes one of the rare occasions when the results of the compartmental modeling of PET data were directly validated by an independent measurement technique (ie, high performance liquid chromatography [HPLC] quantification of samples collected by microdialysis) in humans. The authors therefore concluded that the employed MD/PET combination might be useful during research and development of new drugs, for which knowledge of intracellular concentrations is of interest.

One limitation of MD is that it provides only focal information of neurochemical events. A combination of neuroimaging for neurochemical and neurophysiological monitoring, as used in many clinical centers, and clinical MD might help obtain a broader picture of brain injury and metabolism. The MD/PET combination, although not used for this purpose in humans so far, has the potential to exactly explore and describe the fate and pharmacokinetics of a drug in the body. Exploiting the strengths of both approaches appears to be a straightforward way to predict drug action and therapeutic success and may be used for decision making in drug research and development in the future.

## CONCLUSION

The use of MD and imaging techniques in human drug tissue distribution studies has highlighted inherent strengths and shortcomings of these techniques (Table 1). MD is a comparably cheap method, which is not bound to a research center with sophisticated technology and should be preferred over traditional techniques for the assessment of interstitial drug concentrations and tissue distribution. Provided with the availability of a suitable analytical assay to quantify the drug of interest, and an appropriate ethical setting, physicians can perform MD for virtually any drug molecule. Extensive skills in MD probe placement are not necessary as the insertion process is similar to standard intramuscular or subcutaneous injections. However, experience and individual probe calibration are required for converting dialysate concentrations into absolute tissue concentrations. Besides the measurement of the parent compound, metabolite monitoring is feasible. Issues such as radioactive waste handling and radiation exposure of patients/volunteers and clinical staff are not relevant, as radiolabeled compounds are usually not used. One major limitation is that some tissues and organs such as brain, lung, or liver might only be accessed in combination with surgical procedures.

Nuclear imaging techniques and MRS, on the other hand, are fully noninvasive and are suitable for drug concentration measurements in virtually any organ. MRS imaging has a rather low spatial resolution. In contrast, PET offers excellent spatial resolution in the order of a few millimeters, which enables the assessment of regionally different drug concentrations in a given organ. MD is a focal sampling method and provides concentration measurements in a rather small volume of tissue, defined by the position of the MD probe, with a temporal resolution of 10 to 20 minutes. PET cannot provide chemical resolution (ie, bound and unbound drug or parent drug and metabolites give the same signal). Therefore, PET imaging should preferably be applied to metabolically stable analytes or substances without known tissue retention of metabolites. MRS can resolve metabolites and bound/unbound drug owing to chemical shift differences. Both PET and MRS, however, are not able to discern drug concentrations in different compartments in a given volume of tissue (eg, intracellular, extracellular, intravascular). A limitation of PET of particular relevance for studies that aim at PK measurements over longer periods is the short half-lives of the available radioisotopes. For MD, continuous sampling has been described for several days with appropriate probes; for PET studies with $^{11}$C-labeled drugs, the maximum possible imaging time ranges around 2 hours. Fluorinated compounds, when labeled with $^{18}$F, allow for extended imaging for up to 10 hours with PET. Fluorine-containing compounds are also the compounds of choice for MRS, owing to the high sensitivity and low natural background of the $^{19}$F nucleus for nuclear MR imaging. However, the percentage of fluorinated drug molecules is rather low, which restricts a broader use of both techniques in drug distribution studies. Because MRS does not involve patient radiation exposure, measurements can be repeated over prolonged time periods of up to several weeks.

In conclusion, several novel techniques are currently available for assessing drug distribution and tissue pharmacokinetics in humans. Each of these techniques has proven its ability to provide new information on drug distribution for already marketed compounds but each technique can potentially provide valuable information during drug research and development. The choice of technique or the complementary combination should be based on the compound of interest, the region of the body where distribution and tissue concentrations should be monitored, and the availability of technical and financial resources.

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