

Application of SPECT to the In Vivo Measurement of Benzodiazepine Potency

Two rapidly-growing areas for the development of imaging techniques are the quantification of in vivo receptor binding and the evaluation of pharmacotherapeutic regimens. In this issue of the *Journal*, Innis et al. (1) have described a technique that may pertain to both of these applications. Using a nonquantitative imaging procedure, they have obtained curves for the in vivo displacement of a radioiodinated benzodiazepine (BZ) receptor ligand (Ro 16-0154) by the parent ligand as well as various other BZ receptor-binding agents. This technique was used to determine the in vivo ED₅₀ values for five drugs (agonists and antagonists) that act at the BZ receptor.

The work by Innis et al. demonstrated a correlation coefficient of $r = 0.92$ between the in vivo ED₅₀ doses and the in vitro K_i concentrations. This is a fortuitous result that is rarely seen. The BZ receptor-selective uptake and retention of ¹²³I-Ro 16-0154, as well as its rapid displacement by competitive ligands, are remarkable. The in vivo binding behavior of neuroreceptor ligands depends upon such parameters as the tracer's permeability-surface area (PS) product (2) as well as its arterial input function. These parameters have no impact on receptor binding in vitro, so, for example, the PS product may vary enormously between two agents which have identical in vitro K_i values. PS values and brain extraction have been shown to depend on the lipophilicity of drugs (3). A low brain extraction will alter a drug's arterial input function and cause a higher ED₅₀ value.

One could envisage differences in ED₅₀ values for two ligands of equal in vitro K_i when one agent is highly extracted in the lung and metabolized, whereas for the second agent, the unaltered drug is quantitatively delivered to the brain.

In view of the tracer kinetics and instrumentation required, the potential of ¹²³I-Ro 16-0154 for assay of BZ receptors in the clinical setting is promising. Only a single dose of the radioligand is required for determination of the ED₅₀ of a drug, so the patient radiation burden is minimized. Moreover, the only stringent instrumentation prerequisite is camera linearity. Although it was not demonstrated in the work of Innis et al., the receptor-mediated uptake and retention of ¹²³I-Ro 16-0154 would be anticipated to be altered in pathogenic processes that involve changes in BZ receptor numbers, such as epilepsy (4) or hepatic encephalopathy (5). Thus, SPECT imaging of the distribution of this tracer may provide diagnostic information. Receptor changes can be detected by SPECT only in a qualitative fashion. However, such data may be sufficient for diagnostic use, and clinical procedures with SPECT would be streamlined since complex models to quantify tracer kinetics are not employed.

Aside from this diagnostic potential, the technique described by Innis et al. may be used to derive pharmacokinetic data for patients undergoing therapeutic interventions. Parameters such as the rate of drug delivery to cerebral BZ receptor sites and drug potency (ED₅₀) can be determined within the clinical environment in a noninvasive manner. Thus, patient pharmacotherapy can potentially be individualized in terms of drug selection and dosage regimen. Note that such evaluation is not without some error; the presence of spare BZ recep-

tors reduces the precision of drug potency estimates.

Perhaps of even greater potential utility is the application of this imaging technique for the preclinical evaluation of novel drug entities. The technique described would allow a pharmaceutical manufacturer to rapidly evaluate a series of drugs by means of a noninvasive primate model, which is more likely to approach the human situation than the rodent models typically used for examination of pharmaceuticals. This is particularly important due to the fact that large differences in metabolic pathways can occur between rodents, human and non-human primates (6-8).

The importance of imaging techniques in the evaluation of ethical drugs can be seen from a recent symposium on the topic of "Nuclear Imaging in Drug Discovery, Development and Approval" (9). It is simpler to develop a single radioactive probe for a site of action common to a drug family, as Innis and his colleagues have done, and investigate nonradioactive drugs that act at this site rather than to prepare radiolabeled versions of several drugs. Radiolabeled derivatives are often inappropriate because when labeling a drug, one is constrained by the radioisotopes that can be used. This is because even a fluoro-for-hydrogen replacement produces an analogue of the original drug that will have different lipophilicity, metabolism, etc. By contrast, through application of radiolabeled probes that bind to specific receptor and/or enzyme sites, a large number of new drugs that act at these sites can easily be evaluated in both nonhuman primates and human subjects. Innis et al. have shown that such data can be obtained with a radioiodinated ligand and inexpensive detection systems. This would be an advan-

Received May 29, 1991; accepted May 29, 1991.

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tage in the research setting over the use of relatively expensive positron emission tomography and complex modeling.

These investigators have shown an elegant way for determining the in vivo potency of intravenously-administered benzodiazepine drugs. The bioavailability of drugs given by the more common oral route of administration differs dramatically from the intravenous route, however. Thus, the exact relevance of the in vivo potency following intravenous administration would need to be determined for this technique to achieve widespread application in the clinical and pre-clinical examination of drugs.

Besides the demonstration of these important principles, the paper by Innis and co-workers gives an important caveat to the many investigators working in the area of receptor imaging. A dependence of the clearance of brain radioactivity on body temperature was noted, in which the barbiturate sedative that was utilized lowered body temperatures and decreased radiotracer clearance. The clearance could be altered by maintaining body

temperature at 36°–37°C with a heated circulation blanket, rather than allowing the temperature to drop to 32–34°C due to the action of pentobarbital.

This observation points out the necessity for careful review of the pharmacological effects of drugs used in test animals or human subjects, even when such drugs do not act directly at the receptor targeted by the radiotracer. This is important not only in the relatively controlled research environment, where decisions on anesthetic selection and route of administration impact tracer kinetics, but also in the clinical setting, where the pharmacopeia of drugs used for patient therapy are anticipated to induce as yet unrecognized iatrogenic alterations in the behavior of receptor-binding radioligands.

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