Drug development parameters for functional imaging in neurosciences

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Abstract

State-of-the-art radioactive drug development has become a helpful tool in new functional imaging technologies in neurosciences. Drug development programs are evaluated in terms of effective biodistribution, costs and time. This article details the existing drug development parameters for neuroimaging and highlights some examples, as in Parkinson's disease, alcoholic neuritis and psychotic diseases, showing the benefit and the potential of using new functional neuroimaging technologies for specific studies of the central nervous system.

Keywords: Drug development – Functional imaging – Neurosciences

Introduction

During the past two decades, the reduction in the development of drugs for neuroimaging has resulted rather from unsuccessful drug metabolism studies than from drug studies related to late stage applications of these drugs to animals or humans [1]. The benefit for using new drugs for neuroimaging can be seen by comparing rates of attrition, i.e. rates of losses of drug projects during the late stage of clinical applications. Frank and Hargreaves (2003) in a comprehensive review, presented an interesting survey of pharmaceutical companies comparing reasons for attrition between 1991 and 2000 [1]. This survey revealed a large reduction in losses to pharmacokinetic failures.

Key goals of biomarker developments are to reduce the aforementioned attrition of drugs during clinical phases of their applications, and enable reduction in risks, ensure drug safety and efficacy and reduce overall costs of drug development. The aim of this article is to highlight the importance of functional imaging by a special type of biomarkers used for drug development in neurosciences.

Drug development parameters for neuroimaging

The National Institute's of Health, "Biomarkers and Surrogate Endpoint Working Group" [2] has defined a *biological marker* or *biomarker* as a characteristic that is objectively measured and evaluated as "an indicator of normal processes, pathogenic processes, or pharmacological responses to a therapeutic intervention". A *clinical endpoint* is a characteristic or a variable that reflects how a patient feels or functions, or how long a patient survives. And a *surrogate endpoint*, also called type II marker, is a biomarker intended to substitute for a clinical endpoint: The clinical investigator uses epidemiological, therapeutic, pathophysiological, or other scientific evidence to select a surrogate endpoint that is expected to predict clinical benefit, harm, or lack of benefit or lack of harm. Biomarkers can be categorized into three distinct categories on the basis of their contribution to the logic of a clinical plan. Although these categories seem to parallel analogous phases of drug development, the objective is to deploy them as early as possible. These three phases of drug development are: first to confirm hitting the target and then whether after hitting this target the pathophysiological mechanism of drug function is altered and consequently the clinical status. Biomarkers have become increasingly important for drug development; functional imaging of the brain represents an essential type of biomarkers for the drug development process in neurosciences.

Which technologies are available today in order to look inside the brain? Neuroimaging in drug development can be divided into the following interrelated categories: a) Structural imaging, b) Functional imaging: b1) Neuroreceptor mapping, b2) Metabolic mapping and b3) Functional mapping.

It seems that the key instrument for drug development is not structural imaging, e.g. computed tomography (CT) or magnetic resonance imaging (MRI), but functional neuroimaging, including neuroreceptor mapping. Let us describe the three types of functional imaging mentioned above: b1) Neuroreceptor mapping, e.g. using positron emission tomography (PET) or single-photon emission tomography (SPET) tracers, is utilized to examine the involvement of specific neurotransmitter systems in central nervous system (CNS) diseases, also drug occupancy characteristics and the potential mechanisms of action. b2) Metabolic mapping, e.g. using 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET or magnetic resonance spectroscopy (MRS), is deployed to provide evidence of central activity and the neuroanatomy of drug effects. b3) Functional mapping, e.g. using ^{18}F-FDG-PET or functional MRI (fMRI), is defined to examine disease-drug interactions. Metabolic and functional mapping are sometimes characterized "finger-

printing" for their potential use as clinical screens for new developed drugs.

Incorporating functional neuroimaging endpoints into drug trials, has been triggered by the technological progress of hardware and software, which has found a dramatic development in Nuclear Medicine within the last 50 years, resulting in high-tech products like combined PET/CT or SPET/CT scanners. One of the major advantages of SPET/CT over PET/CT is cost and radiation exposure. Another pro for SPET/CT can be found within the routine radiopharmaceuticals used e.g. ^{99m}Tc with a half-life of 6 h and ^{123}I with a half life of 13 h versus ^{18}F with a half life of 110 min and ^{11}C of 20 min. The major disadvantage of SPET/CT over PET/CT is the inferior image quality due to lower image resolution and sensitivity.

Albeit only a small number of biomarkers assessing the effects of drugs on the CNS is validated and many of these biomarkers are still under investigation, there is growing evidence from clinical research showing the important contribution of functional neuroimaging to particular aspects of CNS disease. Common examples are: Parkinson's disease, alcohol craving, antipsychotics, chemotherapy-induced nausea and vomiting, to name only a few.

In Parkinson's disease, during cognitive performance in a cerebral perfusion SPET study Catafau et al (2000), have shown that retard L-DOPA induces higher frontal activation than standard L-DOPA [3]. In another regional cerebral blood flow study, in alcohol craving also Catafau et al (1999) showed that changes in chronic alcoholic patients in the amygdala induced by naltrexone (opioid antagonist) challenged during detoxification, could be detected [4]. In depressive disorders, a study with the antipsychotic, partial 5HT1A antagonist pindolol, showed and explained why, formerly used doses in clinical studies [5] were insufficient to produce adequate clinical responses [6]. In chemotherapy-induced vomiting and nausea, a receptor occupancy study on aprepitant, a neurokinin-1 (NK1) receptor antagonist used for chemotherapy-induced vomiting and nausea, showed that the dosage regimen of the aprepitant could easily be determined with PET studies using the NK1-receptor tracer [^{18}F]SPA-RQ [7].

The importance of drugs developed for functional neuroimaging can be summarized as follows: a) Intelligent neuroimaging endpoints can minimize risks in drug development at early stages by providing appropriate evidence of drug pharmakcokinetics and the mechanism of their action. b) Go-/no go-decisions and drug dosage can also be inferred from these techniques, which decreases time and especially costs in drug development. c) There is growing evidence that the contribution, the pitfalls, and the potential of neuroimaging related to particular aspects of drug development process, supports the rationale for their clinical application.

Bibliography

1. Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. *Nat Rev Drug Disc* 2003; 2: 566-580.
2. Atkinson AJ, Colburn WA, DeGruttola VG et al. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001; 69: 89-95.
3. Catafau AM, Martin JC, Pascual-Sedano B et al. Retard L-Dopa induces higher frontal activation than standard L-Dopa during cognitive performance in Parkinson's disease. *J Nucl Med* 2000; 41: 219-220.
4. Catafau AM, Etcheberrigaray A, Perez de los Cobos J et al. Regional cerebral blood flow changes in chronic alcoholic patients induced by naltrexone challenge during detoxification. *J Nucl Med* 1999; 40: 19-24.
5. Perez V, Soler J, Puigdemont D et al. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Arch Gen Psychiatry* 1999; 56: 375-379.
6. Rabiner EA, Bhagwagar Z, Gunn RN et al. Pindolol augmentation of selective serotonin reuptake inhibitors: PET evidence that the dose used in clinical trials is too low. *Am J Psychiatry* 2001; 158: 2080-2082.
7. Hargreaves R. Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. *J Clin Psychiatry* 2002; 63: 18-24.