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Measurement of CNS Effects

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INTRODUCTION

The measurement of CNS effects is particularly relevant for a new drug, not only when this drug is supposed to exert a psychotropic effect, but also for drugs acting on other systems for which possible side-effects or adverse reactions at the level of the CNS need to be investigated and assessed at the earliest stage of development.

Clinical observation and follow-up of subjects administered with a new drug in Phase I and early Phase II will provide very superficial information on the appearance of manifestations such as sedation, drowsiness, sleepiness, excitation, irritability, insomnia, etc. More in-depth assessment of CNS effects demands the use of more structured and objective techniques.

CNS effects can be classified, for practical and descriptive reasons, in terms of effects on behaviour, on vigilance/attention and cognition, on neurophysiological activity of the brain and on neuroendocrinological functions. The measurement of each of these classes of effects involves specific techniques and instruments. We shall review these aspects of measuring CNS effects and separate them into four groups: (1) psychometric testing; (2) neurophysiological and psychophysiological measurements; (3) behavioural assessments; and (4) neuroendocrinological measurements.

It has to be stressed that human psychopharmacology has progressed considerably in the last few decades and has moved from the observation of merely behavioural effects along the axis sedation–excitation to very sophisticated techniques specifically and objectively assessing different CNS functions. The aim of modern human psychopharmacology is twofold: to assess and measure possible CNS toxicity of drugs independently of their therapeutic action, and, in the case of drugs supposed to have a psychotropic effect, to give predictive information on the possible therapeutic effect. It is this latter aim which greatly stimulated research in the field of human psychopharmacology in order to improve the therapeutically predictive value of early administration in humans.
Pharmacodynamics seeks to establish the relationship between pharmacokinetics and behavioural measures. Psychopharmacology has as its basic assumption that the effects of a psychoactive drug will be manifested by the changes produced in overt behaviour. Such changes are regarded as more or less independent of any pharmacokinetic measures and variables.

The major task of psychopharmacologists is to develop sensitive, reliable and valid procedures for assessing drug-induced changes in human behaviour. The development of psychometric systems must be done within an appropriate theoretical and methodological framework, and with due regard to the psychophysics of human sensory and response systems. Failure to take adequate account of the theoretical context of a test and failure to consider the psychological aspects and limits of using human subjects invalidate many so-called psychometric ‘tests’ and do not permit any generalisation of findings and results obtained beyond the close confines of a particular experiment. A review of the psychometric tests available in 1980 (Hindmarch, 1980) showed that many did not consider any basic theoretical or methodological aspects of measurement. Many ‘tests’ were ingenious and sometimes whimsical, but these were more likely to be unreliable, invalid and insensitive to the effects of psychoactive drugs.

The advent of the microprocessor has caused a burgeoning of computer-based, ‘automatic’, test systems, the majority of which also fail to consider the essential requirements of validity and reliability. It is not sufficient to create a ‘test’.

A psychometric assessment or measure of drug effects in man requires that a test be constructed and developed according to established theoretical, methodological, psychological and pragmatic standards. Tests without a history of reliable usage and without validation against external norms are of no use to those wishing to investigate the psychoactive effects of pharmaceutical agents. On the other hand, there are several psychometric assessments which have been shown to be reliable and valid measures of the CNS activity of a wide range of drugs, including antihistamines, hypnotics, antidepressants, antianxiety agents and nootropics (Hindmarch, 1980, 1981, 1982, 1983, 1984a, b, 1985, 1986). These tests assess many aspects of information processing, sensorimotor co-ordination, short-term or working memory, reaction time, psychomotor functions related to skill behaviours (for example, car driving) and mental arithmetic and logical reasoning. A judicious selection of different tests reflecting different aspects of CNS functions can be made to form a battery of measures which cover the possible range of activities of putative psychotropic agents.

The tests of psychological performance can be presented on microprocessors, as pencil and paper tasks or on specially designed hardware, with or without computer assistance. The results from such assessments can be augmented with scores from subjective rating scales, which, when properly constructed, can give reliable ratings of sedation and/or arousal (Hindmarch et al., 1980; Hindmarch and Gudgeon, 1982; Gudgeon and Hindmarch, 1983; Hindmarch, 1987), mood (Hindmarch, 1979a, b) and sleep (Hindmarch, 1984a, 1975, 1979c, 1984b).