CLINICAL INVESTIGATION OF HYPNOTIC MEDICINAL PRODUCTS

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This note for guidance is intended to assist applicants in the interpretation of Directive 75/318/EEC as amended with respect to specific problems presented by clinical investigations of medicinal products intended for treating insomnia.

1. INTRODUCTION AND FIELDS OF APPLICATION

While there is certainly a great inter-individual and – thinking of the whole life span – also intra-individual variation in the need for sleep, sleep problems are among the most frequent symptoms presented in medical practice.

Sleep disorders include hypersomnias, parasomnias, sleep-wake-schedule disorders, and – above all – insomnias.

Insomnia has to be regarded as a symptom, not a disease in itself. It may be transient/situational or persistent and is characterised by one or more of the following main criteria:

– difficulties in initiating sleep;

– disorders of maintaining sleep (frequent awakening);

– premature awakening;

– feeling of nonrestorative sleep,

with subsequent impaired daytime functioning.

Insomnia as a leading or accompanying symptom can be associated with various kinds of mental or physical illness (e.g. depression, pain), psychosocial stress (e.g. marital conflicts). Sometimes insomnia is associated with the use of medicinal products (drug dependence insomnia) or alcohol. Sometimes, no basic cause can be identified (primary insomnia).

Very often patients have false or at least exaggerated ideas about the amount of sleep that is necessary. In these cases just information may be helpful.

Whenever possible, treatment of sleep disorders should consist of treatment of the basic underlying illness or psychosocial conflict. Therapeutic intervention by means of hypnotic agents can only produce symptomatic relief, and abuse and dependence may occur.

2. PRECLINICAL CONSIDERATIONS

The usual preclinical studies should be supplemented by studies in animal models indicative of the addictive (dependence producing) potential of the new therapeutic agent.

Three phenomena are considered as related to drug dependence, viz. tolerance, physical and psychic dependence, the latter two being essential. Tolerance is in many cases related to development of dependence, but it is not an essential feature.

2.1 Physical dependence

Development of physical dependence is characterised by manifestation of withdrawal phenomena occurring after discontinuation of medicinal product administration.

There are characteristic patterns of withdrawal symptoms depending on class and mechanism of action of a therapeutic agent.

Early signs of withdrawal are often characterised by changes in REM-sleep duration and autonomic disregulation. Later hyperexcitability and convulsions, tremor and vomiting may occur.

Withdrawal phenomena are easily assessable especially in rats, dogs, and monkeys.

2.2 Psychic dependence

Psychic dependence implies a craving for a medicinal product which is measured by animal drug taking behaviour models.

Assessment of positive reinforcing properties of medicinal products leading to craving is best performed using self-administration techniques in rats or monkeys.

Among the suitable screening methods are the various self-administration techniques which assess generalisation of substance taking behaviour over different classes of dependence producing substances in substance experienced animals.

Continuous self-administration studies using substance naive animals should be performed in addition.

Further assessment of the substance in a substance discrimination paradigm is extremely helpful. Generalisation effects of the agent in animals trained for known dependence producing compounds can be used to classify whether the agent will belong to such a group of compounds.

2.3 Tolerance

Tolerance can be measured and quantified in a number of animal experiments as a decrease of effectiveness of a therapeutic agent. This may be evidenced, after up to four weeks of treatment, by increased vigilance and diminution of depression as well as of toxicity. Further analysis of the mechanism underlying the development of tolerance (metabolic, receptor effects, bio-chemical tolerance) should be performed.

3. STUDIES IN CLINICAL PHARMACOLOGICAL MODELS

Initial studies of a potential hypnotic agent will follow the normal pattern (pharmacokinetics, pharmacodynamics, single and repeated dose tolerance) with the following special features:

3.1 Pharmacokinetics

Pharmacokinetic parameters should be investigated in elderly persons as well as in young adults, since elderly people form an important target population, with altered pharmacokinetic conditions.

Special attention generally should be paid to

– cumulation effects;

– effects of food intake and smoking on absorption and elimination;

– kinetic interactions (e.g. enzyme induction);

– presence, activity and half-life of metabolites;

– pharmacokinetic variability due to genetic polymorphism;

– circadian variation (relevance e.g. for shift workers);

– patients with hepatic and renal insufficiency.

3.2 Pharmacodynamics

Onset, nature and duration of CNS effects should be documented by neurophysiological (EEG) measures and psychometric tests (dose-effect-curves, time-effect-curves).

Again separate studies in elderly people are considered necessary, and again circadian variations in pharmacodynamics should be considered.

Sleep laboratory studies even in healthy volunteers without symptoms of insomnia may be useful in investigating dose response-relationships and performing dose comparisons.

Special risks (e.g. amnesiac effects, especially anterograde amnesia) should be investigated in appropriate experimental models in healthy volunteers (e.g. learning and memory tests after medicinal product intake, memory assessment in the morning after medicinal product intake: selective reminding tests, recognition memory).

4. THERAPEUTIC STUDIES

4.1 Types of studies

Two complementary types of study are used to demonstrate therapeutic efficacy and both are considered necessary.

4.1.1 Sleep laboratory studies permit extensive assessments with electrophysiological as well as psychological methods before, during and after the night, but take place in a kind of artificial setting and, moreover, might be suited to attract "professional insomniacs" due to the fees that often have to be paid in order to compensate for prolonged stay in the laboratory.

4.1.2 Clinical studies in inpatients (e.g. preoperative patients, patients in nursing homes) or outpatients (frequently multicentre general practitioner studies) take place in the natural setting with less extensive measurements.

Separate studies in elderly patients are always considered mandatory. Studies in inpatients or outpatients should be conducted separately.

While the aim of the treatment with a hypnotic medicinal product is always the improvement of subjective parameters of disturbed sleep, these subjective notions can be studied objectively by neurophysiological measurements. The efficacy criteria and measurement techniques for the evaluation of hypnotic effects vary depending on the type of study.

4.2 Efficacy criteria

Corresponding to the initially mentioned criteria of insomnia, the following basic efficacy criteria for hypnotic agents should be evaluated:

– sleep onset latency;

– sleep continuity;

– sleep duration;

– feeling of restorative sleep;

– subsequent improved daytime functioning.

These parameters can be assessed by objective (sleep laboratory) and subjective (self-rating) methods. Thus the measurement techniques for the evaluation of hypnotic effects indicative of therapeutic efficacy include neurophysiological as well as psychometric methods.

4.2.1 Neurophysiological parameters

a) EEG

EEG recordings are made to identify sleep stages via background EEG activity (frequency/amplitude distribution) and pattern recognition (sleep spindles, K-complexes, saw tooth waves, etc.). The signal can be analysed visually (internationally acknowledged classification systems) or automatically (spectral analysis, period analysis).

b) Multiple sleep latency test (MSLT)

Sleep propensity differs with the time of day (circadian effect). Thus the study of hypnotic effects does not have to be restricted to night sleep. Study designs with continuous bed rest or with the MSLT procedure (short sleep recordings every two hours, five times per day) lead to a more complete picture of product effects. Parameters measured are: sleep onset latency, the occurrence of sleep onset REM episodes, and the duration of sleeping during the lights off period.

4.2.2 Psychometric parameters

Psychometric methods aim at the measurement of mood as well as performance as indicators of therapeutic efficacy. The choice of assessment methods should be justified from test quality criteria (reliability, validity, availability of norm data for the population in question).

a) Sleep questionnaires/visual analogue scales

Assessment of subjective feelings of improved and restorative sleep (sleep quality rating) and consequent improved daytime functioning is done by sleep questionnaires and self rating (mood) scales (usually patient diaries).

b) Improved daytime performance

Depending on the type of study (see 4.1) objective psychological performance tests should be performed – not only in the morning but also in the evening of a day after medicinal product intake in order to demonstrate improved intellectual functioning after restorative sleep.

Suitable tests may assess perceptual speed, concentration (e.g. letter cancellation), continuous attention, cognitive speed, information processing. For tests that are prone to

learning and memory effects on repeated administration (e.g. digit-symbol-substitution tasks), parallel forms have to be provided.

4.3 Patient selection

4.3.1 Clinical criteria

The patient selection criteria also depend on the kind of study to be performed, certain clinical criteria being valid for all studies:

The nature of the patient's sleep disorder should be classified according to an internationally acknowledged classification system, e.g. Association of Sleep Disorders Centers, ASDC, The Diagnostic Classification of Sleep and Arousal Disorder; ICD-10, DSM III-R. Further descriptive parameters (estimated sleep latency, number of awakenings, estimated duration of sleep) as well as a detailed history of the insomnia should be documented. It is essential that the inclusion criteria and reason for treatment with a pharmacological agent should be perfectly clear to the reader of the study report.

Homogeneous patient groups are required for the pivotal studies. In order to reduce the amount of variance, patients with primary insomnia and patients with insomnia associated with non-psychotic mental disorders as well as preoperative patients are considered appropriate for such studies. Insomnia associated with major affective or psychotic disorders seems less appropriate because of the amount of intervening variance. (Further evidence for these and other groups of patients can be obtained by investigations in different subgroups, see 6.1.)

Prior and concomitant medication has to be documented in detail. If a placebo wash-out period is successfully accomplished, the need for further treatment with a hypnotic medicinal product has to be made plausible. In evaluating such results, however, regard must be paid to the half life of the substance which is being washed out and to the possibility of withdrawal phenomena.

History of drug or substance abuse is an exclusion criterion.

4.3.2 Neurophysiological criteria

In sleep laboratory studies existing sleep disorders have to be verified by polysomnographic recordings. At least two consecutive adaptation nights are considered appropriate within the diagnostic procedure in order to allow patients to adapt to the unfamiliar laboratory environment. (The same applies to control subjects.)

Visual classification of sleep EEG studies should follow internationally acknowledged rules (Rechtschaffen & Kales). In case of automatic classification systems the validity of classification criteria should be critically discussed.

Besides EG measures, sleep polygraphy includes further descriptive parameters, such as

a) EMG

Surface electrodes are placed in the chin region to identify muscle inhibition during REM sleep.

Recordings from the tibialis muscle allow the identification of restless leg syndrome (RLS) or periodic leg movements during sleep (PMS), sleep dependent organic causes for dementia.

b) EOG

The electrooculogram is essential for the quantification of phasic activity during REM sleep. In addition, the analysis of eye movement and blink activity greatly supports the differentiation between the waking state, stage 1, and REM sleep.

c) Respiration

Apnoeic pauses during sleep should be registered for diagnostic purposes as well as to identify products which induce apnoeic pauses or aggravate already existing sleep apnoea syndromes.

d) ECG

Mean heart rate and variability help in the recognition of sleep arousals and full awakenings.

4.4 Study designs

4.4.1 Sleep laboratory studies

Again – as in the diagnostic phase – at least one adaptation night without medication is considered appropriate, followed by at least one placebo adaptation night. During this run-in phase patients have to be trained on the performance tests in order to control the effects of practice.

For studies intended to formulate hypotheses about a medicinal product hypnotic potential, at least one night for each medicinal product dosage should be investigated by polysomnographic measures.

In order to test adequate therapeutic efficacy by sleep laboratory measures (pivotal studies), multiple nights on medicinal products should be documented (minimum 5-7 days or 7-8 times elimination half-lives for the parent substance or active metabolites).

All studies have to be placebo-controlled. Three armed designs with a reference medicinal product are recommended.

(For the investigation of rebound insomnia and discontinuation phenomena longer treatment phases are necessary, see 5.2.)

4.4.2 Clinical studies

For clinical medicinal product evaluation proper comparison with placebo as well as with a standard product in parallel group designs following an initial placebo-run-in-phase (see 4.3.1) is indispensable for confirmatory analysis. For pivotal studies 2 treatment weeks are considered adequate, as currently available medicinal products are not recommended for longer use (for evaluation methods see 4.2.2 (a)).

For preoperative patients, study protocols should specify drop out criteria.

Dose response-relationships should be established and reproduced in clinical models. The minimal effective dose and the highest recommended dose should be determined.

The sample size should be justified on biometrical-statistical criteria. Biometrical analysis should include standard as well as intent-to-treat analysis.

Cross-over designs are generally not recommended because of their risk of uncontrolled carry over effects. If this kind of design is chosen, it should be especially justified by

demonstrating that certain statistical requirements are fulfilled (exclusion of interaction effects).

Compliance controls as well as screenings for other additional illicit psychotropic substances are recommended. This refers to the initial placebo run-in period and the shift to the active substance as well as to treatment and placebo discontinuation phases (see 5.2.3).

5. SAFETY ASSESSMENT

5.1 Monitoring of unwanted effects

5.1.1 ADR

Adverse events occurring during the course of the treatment (e.g. blood dyscrasias, liver, kidneys, gastro-intestinal tract) should be carefully recorded, with particular regard to psychological and neurological changes (e.g. those involving gait, speech, co-ordination, nystagmus, lethargy, amnesia). Neuropsychological tests should be applied accordingly. Adverse reaction scales should be standardised for use in studies with psychotropic substances. Clinical observations should be supplemented by appropriate laboratory tests and cardiological recordings.

5.1.2 Hang-over effects

Hang-over effects are defined as decreased vigilance and impaired concentration the morning after product intake. The experimental setting of sleep laboratory studies allows for the careful investigation of possible effects by psychometric tests (mood scales, concentration and attention tests, simple arithmetic procedures, vigilance tests, e.g. critical flicker fusion) as well as by means of EEG recordings (including MSLT). Special attention should be paid to:

5.1.3 Effects on driving and operating machinery

This is important standard information for every summary of product characteristics (SPC) and package insert. Electrophysiological (EEG-) measures of vigilance-indicative variables (e.g. delta power, alpha slow wave index, slowing of the dominant occipital frequency, anteriorisation of the basic rhythm in the occipital field to the frontal region, onset of frontal subvigil beta bursts) and psychological vigilance and performance tests, psychomotor test batteries (pursuit rotor, tracking tasks, pegboard), reaction tests (simple and choice reaction time) as well as car-driving simulators and standard over-the-road driving tests are considered appropriate to determine whether a hypnotic medicinal product may impair vigilance and psychomotor functions the day after medicinal product intake. As motivational factors can affect the results in those tests, the duration should be long enough (minimum one hour) because of well-known time-related compensatory skills of subjects – especially in task situations with high intrinsic motivation (e.g. car driving simulators).

Placebo as well as positive controls are necessary in these studies in order to avoid false negative results due to inadequate models.

However, the limited value of experimental models for the extrapolation to real life situations should be critically discussed.

5.1.4 Overdosage

All available – pharmacological and clinical – information concerning symptoms and therapeutic measures in accidental overdosage or deliberate self-poisoning should be provided. Sponsors and clinical investigators should be prepared with an emergency protocol as well as suitable case record forms to start certain studies (e.g. pharmacokinetic determinations) immediately under the circumstances of accidental or deliberate overdose.

5.2 Dependence potential

For ethical reasons there are only very limited models to investigate the dependence potential of a new therapeutic agent in humans. But there are several other phenomena which may be considered as indicative of a drug abuse potential:

5.2.1 Mood and/or behavioural changes

Alterations in healthy volunteers' or patients' mood and behaviour after medicinal product intake should be carefully investigated. Special attention should be paid to signs of euphoria.

5.2.2 Development of tolerance as an indicator for dependence potential

Tolerance can be defined as a decrease in specific pharmacodynamic (sedative-hypnotic) effect and usually will lead to an increased dosage. It is detectable by careful surveillance of patients' diaries.

5.2.3 Discontinuation phenomena as an indicator for dependence potential

Discontinuation phenomena and rebound effects may be considered as other indicators for a medicinal product dependence potential. Therefore every sleep laboratory or clinical study should end up in a placebo discontinuation phase, the length of which is determined by kinetic parameters and the length of the preceding treatment phase.

It is mandatory that each night (starting with the first night of the placebo discontinuation phase) will be analysed separately, especially when studying short-acting agents. Combined analysis over two or three nights may result in levelling-out of disturbances occurring during the first night only.

As discontinuation phenomena are less probable after short term treatment, at least some special studies should be performed after a four weeks' exposure. Careful attention should be paid to detailed assessment of symptoms by subjective and objective rating scales (symptom checklists, questionnaires). Baseline data (pre-treatment values) as well as scores during treatment should be available. In sleep laboratory studies it is advisable that the patient attend the lab again for a control night at the end of the four weeks' treatment phase and for the following single blind placebo discontinuation phase.

Usually it is difficult to differentiate discontinuation phenomena from symptoms of persisting insomnia: they resemble each other closely. These problems should be critically discussed with reference to baseline values.

Discontinuation phenomena related to the use of hypnotics are associated with “pill-taking” phenomena. It is recommended to do some studies with a discontinuation phase without placebo, which situation will reflect the usual practice.

Moreover, as personality characteristics may be of importance to both the development of dependence and the severity of withdrawal, personality characteristics should be taken into account in these trials.

5.3 Long-term studies

Treatment with hypnotics usually should not exceed a few weeks. However, as treatment of chronic sleep disorders often exceeds the recommended short term therapy, Long-term data (at least six months) are considered necessary, provided the medicinal product seems to be free of dependence potential.

The patient eligibility criteria for these Long-term studies should be defined with special care.

As currently available standard medicinal products are not recommended for prolonged use, standard controlled studies are not possible for ethical reasons. Therefore only open Long-term studies seem feasible at the moment, which require careful reflection of the limited prognostic value of such studies.

5.3.1 Safety data

These should relate in particular to effects on clinical-chemical parameters, especially liver function (enzyme induction) and haematological parameters.

5.3.2 Efficacy data

Sustained therapeutic efficacy without development of tolerance has to be documented.

6. SPECIAL STUDIES

6.1 Studies in special groups of patients

The need for separate studies in special groups of patients who may be at increased risk should be considered. As mentioned before, studies in elderly patients are mandatory (see also *Clinical Investigation of Medicinal Products in Geriatrics*).

Clinical investigations of a hypnotic medicinal product in children have to be performed in separate studies if the claim pertains to the treatment of this target population (see note for guidance *Clinical Investigation of Medicinal Products in Children*).

6.2 Interaction studies

6.2.1 Interaction with alcohol

With currently available hypnotics, concomitant intake of alcohol will lead to an additive or even potentiated depression of the CNS, and to more or less severely pronounced sedation. This will be relevant for driving and operating machinery and correspondingly will require warnings in the summary of product characteristics (SPC) and package insert. For safety reasons investigation is required as to whether concomitant intake will lead to more sedation than intake of one of the components alone. Neurophysiological (EEG) and

pharmacopsychological methods (performance tests, self rating scales) would be considered as appropriate.

6.2.2 Interaction with CNS-active products

Other psychotropic or CNS-active products such as antidepressants or neuroleptics are likely to be given to psychiatric patients simultaneously with hypnotics. Therefore interaction effects should be investigated, not only in pharmacokinetics, but, as the clinical relevance of for instance altered serum levels is often unknown, also in clinical models and in patients.

6.2.3 Interaction with cardiac medicinal products

Frequently insomnias occur in elderly patients who suffer from multiple diseases simultaneously. As cardiac disorders and thus concomitant treatment with cardiac medicinal products are very common in elderly patients, interaction effects should be investigated.

6.2.4 Interaction with antirheumatic medicinal products

Elderly patients as a main target population for hypnotic medicinal products often suffer from various rheumatic diseases – pain and/or prolonged daytime rest/immobilisation being one of the possible reasons for sleep disorders.

Therefore it is considered important to study interaction effects between hypnotics and antirheumatic medicinal products, if there are pharmacological reasons to expect interaction effects.

6.3 Cardio-respiratory effects/Sleep apnoea studies

Hypnotics affect the respiratory control mechanisms in a dose-related manner. Thus the respiratory parameters, e.g. tidal volume, minute ventilation or ventilatory response to CO_2 challenge should be investigated as a matter of routine. Non-invasive monitoring methods such as inductive plethysmography performed during sleep or exercise allow the registration of ventilatory events even in an ambulatory approach.

Sleep polygraphic recordings should include measurements of nasal and oral airflow and abdominal breathing excursions.

6.4 Neuroendocrinological parameters

Depending on the pharmacological properties of the new therapeutic agent, the investigation of neuro-endocrinological parameters (e.g. growth hormone) may be necessary.