

Sedation: A Non-Specific Phenomenon

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ABSTRACT:

SEDATION : A NON-SPECIFIC PHENOMENON

Sedative molecules are defined as substances that decrease, often in correspondence to dose increase, psychomotor performances in animals as well as in humans. These substances are psychotropic drugs that belong to the hypnotic, neuroleptic, anxiolytic, antidepressant and antihistaminic family. In the clinical situation, sedation is an undesirable secondary effect after the utilization of these drugs. It is for this reason that sedative drugs are used in pre-anaesthesia or agitation, or even aggressive phenomena. The purpose of this article is therefore to highlight the different pharmacodynamic and pharmacokinetic properties of drugs which can be used to induce sedation.

Key Words: Sedation, neuroleptics, hypnotics, adverse effect

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INTRODUCTION

The concept of sedative drugs doesn't correspond to an exact pharmacological action. Sedative molecules are thus defined as substances that decrease, often in correspondence to dose increase, psychomotor performances in animals as well as in humans. These substances are psychotropic drugs that belong to the hypnotic, neuroleptic, anxiolytic, anti-depressant and antihistaminic family.

Often in the clinical situation, sedation is an undesirable secondary effect after the utilization of these drugs (1). It is for this reason that sedative drugs are used in pre-anaesthesia or agitation, or even aggressive phenomena.

The purpose of this article is therefore to highlight the different pharmacodynamic and pharmacokinetic properties of drugs which can be used to induce sedation.

MEASURE OF SEDATIVE ACTIVITY IN ANIMALS

Measure of the spontaneous motor activity (actimeter)

Motor activity is classically studied with the actimeter of Boissier and Simon (2). Under normal conditions a dose-effect relationship exists, i.e. as the dose increases the animals move less and less resulting in sleep. Locomotor activity is measured by the crossing of the photocell activity meter and automatically recorded.

Certain substances such as alprazolam, can at a lower dose increase the locomotor activity in mice whereas when the dose is increased a sedative effect is observed (3). It has been shown that the alpha-1 adrenergic receptor antagonists and alpha-2 receptor agonists can decrease the spontaneous locomotor activity (3).

Stimulating drugs such as amphetamines, can appear to decrease locomotor activity while inducing stereotype movements interpreted as hyperactivity (the modern actimeter can take into account such a phenomenon).

Potentialisation of barbiturate effects

Drugs are administered intraperitoneally 30 minutes before a hypnotic dose of pentobarbital or sodium barbital. The delay between drug administration and the suppression of the righting reflex for each mouse is noted. The difference between these 2 figures represents the sleep time.

Some differences exist between drugs, some increase the sleep-time induced by both substances in our experience, those substances which potentiate these two barbiturates are clearly sedative drugs.

MEASURE OF SEDATIVE ACTIVITY IN HUMANS

Digit-Symbol Substitution Test (DSST)

This test evaluates sensory information recogni-

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tion. In order to limit the learning phenomenon, several equivalent versions exist, permitting its utilisation for repeated measures in the same individual. On the top of a sheet there is a list of symbols to be substituted for a digit (0 to 9). The subjects are required to complete as many digit-symbol substitutions in 90 seconds by writing down the appropriate symbol. The number of correct substitutions is scored.

Choice Reaction Time (CRT)

This test is used to assess sensorimotor performance. It is generally performed by means of the Leeds Psychomotor tester, constituted of an automated electronic picture apparatus. Subjects are required to extinguish one of six red lights presented in a semicircle and randomly illuminated by touching the appropriate response plot. The mean score of two parameters are automatically tested by LPT: (1) the latency of the perception to the visual stimuli (Recognition Reaction Time-RRT), (2) the time taken to extinguish the light (Motor Response Time-MRT).

Critical Flicker Fusion (CFF)

This test assesses central integrative capacity. On the screen of the Leeds Psychomotor tester, at a distance of 1 meter from the individual, 4 red flashing diodes appear at an increasingly rapid frequency. At a certain frequency, the signal appears as a continuous light i.e. they are fused. The frequency (measured in Hertz) at which the lights seem continuous is recorded for each subject. Simultaneously, the frequency corresponding to the passage of the continuous light to the flashing light is recorded. Individual thresholds are determined by the psychological method of limits on three ascending and three descending values.

Subjective assessment

At the end of the evaluation, subjects self-assess their feelings by placing a mark across a series of three Visual Analog Scales (which are not graded) of 100-mm lines with opposite statements at each end (e.g., calmness/agitation, tiredness/dynamism, improvement or deterioration of concentration capacity). Scores are measured in millimetres from the middle of the lines of the mark.

Side effects questionnaire

This self-evaluation checklist of 26 items (e.g. nausea, blurred vision, change in appetite, dizziness, headaches etc.) is given to subjects to record the frequency and severity of side effects from the treatment.

Numerous studies have shown the secondary effects of benzodiazepines used as anxiolytics or hypnotics in psychometric performances (5,6). Buspirone

(a non-benzodiazepine anxiolytic) presented as a non-sedative compound, induces the same psychomotor alterations as those of benzodiazepines in healthy volunteers (7).

SEDATIVE ACTION OF GABA-ACTING SUBSTANCES

The action of barbiturates is similar to that of benzodiazepines in that they increase GABAergic neurotransmission. However some differences exist. Benzodiazepines increase the frequency of the opening of the chloride ion channel whereas barbiturates increase the duration of channel opening (8).

High doses of barbiturates, (in contrast to benzodiazepines), have a direct action on the chloride channel in the presence or absence of GABA (9).

A correlation between the percentage of receptor occupancy and the therapeutic activity of benzodiazepines has been established. 20% occupancy results in an anxiolytic action, 40% in a sedative action and 60% in a hypnotic action. This may explain the relatively modest therapeutic index of these molecules insofar as an overlap exists between the doses inducing an anxiolytic effect and that results in a sedative effect.

Furthermore, the speed of resorption of benzodiazepines determines their sedative effect and probably their speed of penetration into the central nervous system. For example, chlorazepate used at 10mgs is more sedative than the same dose of prazepam. These two molecules are pro-drugs with the same metabolite, desmethyldiazepam, however the speed of transformation for chlorazepate is one hour whereas it is three hours for prazepam (10).

NEUROLEPTIC SEDATIVE EFFECT

In French psychiatry practice, neuroleptic sedation is considered different to the sedation induced by tranquilizers. However, the notion of neuroleptic sedation is considered too blurry and ambiguous and a specific action against psychotic anxiety rather than a sedative effect has been suggested. Sedation in neuroleptic treatment would thus be due to an excess effect on psychotic anxiety, rather like the anxiolytic effect of benzodiazepines can result in a hypnotic effect at higher doses (11).

This sedative effect of neuroleptics has sometimes been considered as a therapeutic-like action sometimes a side effect. For example, in the classification of Delay and Deniker of 1961 (12), the somnolence effect that can be considered as an extreme sedative effect is categorized under the side effects of neuroleptics (12).

However, in a more recent classification (13), the sedative effect is a major therapeutic effect, associated with an anti-productive and anti-negative effect.

The sedative effects of neuroleptics are most often attributed to their alpha-adrenergic action (alpha-1).

This is especially true for the phenothiazines (14). However, according to Richelson (15), the affinity of certain neuroleptics for histamine receptors (type H1) would explain the sedative action for these derivatives. Thus, schematically, the most histaminergic and adrenergic substances are the most sedative in humans (16).

According to Curry *et al.* (17), the sedative effect of neuroleptics depends on:

(1) the receptor binding profile of the molecule, (2) plasma concentration, and more specifically the level in the cerebrospinal fluid (18).

However, other authors consider that sedation isn't directly linked to plasma concentrations. There are those who also consider that neuroleptic sedative effects appear at lower dose utilization (non-antipsychotic dose) in the non-psychotic patient (16).

Despite the significant literature, the dose relationship effect, plasma concentration and therapeutic effect is not clearly established with regard to the neuroleptics. These are dependent on the moment of neuroleptic administration in relation to the beginning of the treatment. Indeed, Wolf and Villeneuve (14) showed that somnolence was often observed in the first days or weeks of neuroleptic treatment.

ANTIDEPRESSANT SEDATIVE EFFECT

In France, in a global antidepressant treatment approach, the sedative effect is an integral part of the treatment. Until recently, it was obligatory to ensure a sedative effect at the beginning of antidepressant treatment through benzodiazepine or a sedative neuroleptic (e.g. levopromazine) association as it was feared that the loosening of psychomotor function failed to occur before mood and anxiety disorder were ameliorated. The suicidal risk was thus decreased due to the loosening of psychomotor function. In North America the association of benzodiazepine and antidepressant as part of the treatment in depressed patients has been considered as a big mistake. The reason is due to the risk of the disinhibiting effect by benzodiazepines, incriminated in "passage to the act" cases. English and German doctors are in agreement with this point of view. In France, sedative association is not always necessary since antidepressants are efficient in anxiety and sleep problems seen in the depressed patient from onwards of 8-10 days of treatment.

The intrinsic sedative action of a drug is desirable in cases where the anxiety and insomnia are of the first order. One can imagine that anxiodepressive syndromes of the next DSM IV, already taken into account in French classification, will indicate an antidepressant with sedative properties.

When sedation is considered as a side effect, one realizes that it can be observed with nearly all anti-

depressants. It is observable in about 10 to 30% of patients treated with antidepressants with the exception for the secondary amines (TCA class) for which this side effect is observed in only about 2% of cases (19). This side effect, when it is intolerable or extreme, can be a reason for antidepressant interruption and therefore must not be neglected.

In other antidepressant indications such as the phobic states, obsessive and compulsive disorders, panic disorder as well as the chronic pain syndrome, it is difficult to judge sedative effect. In regards to the pain phenomena, Boureau *et al.*, (20), in their literature review failed to mention a particular antidepressant sedative activity, as one would have expected, they rather remarked on an antidepressant efficiency with a particular serotonergic activity.

Amitriptyline is sometimes (Laroxyl®, Elavyl®) prescribed as a hypnotic at a dose of 25 mg taken at bedtime.

The sedative action of antidepressants is often associated with their activity on histaminergic H1 receptors. However, in the case of mianserin (Athymil®), the sedative action is assigned to an alpha antagonist effect.

Among tricyclic antidepressants with notable sedative activity, the secondary amines possess particular potency. The action of Trazodone is equally noted.

ANTIHISTAMINERGIC DRUGS

Central H1 receptor blockade leads to sedation. The majority of phenothiazine neuroleptics possess this property (with or without an alpha-1 adrenergic receptor antagonist effect).

The most sedative antihistamines are: dimenhydrinate, diphenylhydramine, promethazine and trimiprazine. The latter two also have a potent anticholinergic action.

Generally these compounds are highly metabolised with a relatively short half-life, but their pharmacokinetics remains unknown, as most were developed before the introduction of pharmacokinetics (21).

CONCLUSION

Compounds possessing sedative effects are numerous and include all drugs having an action on the GABAergic transmission, alpha-1 adrenergic receptors, cholinergic receptors and on histaminergic H1 receptors.

The pharmacodynamics of these derivatives permits animal or human psychomotor performance studies without the utilization of a certain action specific test. A more or less specific action is identified by interaction studies.

The pharmacokinetic studies have shown that it is often necessary to obtain a rapid peak effect (a high concentration), with the exception of the antidepressants.

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