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Pharmacological differences of GABAergic compounds: a pharmacodynamic characterization

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Citation

Haas, S. L. de. (2008, October 30). *Pharmacological differences of GABAergic compounds: a pharmacodynamic characterization*. Department of Clinical Pharmacology, Centre for Human Drug Research, Faculty of Medicine, Leiden University Medical Center (LUMC), Leiden University. Retrieved from <https://hdl.handle.net/1887/13261>

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SECTION 3



SUMMARY AND CONCLUSIONS

CHAPTER 11

Discussion and conclusions

In this thesis, a series of studies is described that explored different pharmacological and therapeutic effects of novel GABAergic and GABA-like agents in humans. These novel agents have been developed to fulfil the need for more CNS treatments that show an improved side-effect profile compared to the current treatments.

The first section of this thesis shows the pharmacodynamic effects of several selective (partial) agonists in healthy volunteers using a validated CNS battery. Inclusion of this battery in early phase drug development may enhance the understanding of the efficacy and/or safety of new chemical entities in clinical development. For benzodiazepines, the effects on these pharmacodynamic measurements are known very well, and comparison to these could be very helpful to investigate the differences between traditional and newly developed agents. The clinical relevance of all measurements is not clearly established, although correlations with different effect parameters have been reported for benzodiazepines [1].

Chapter 2, 3, 4 and 5 showed that most selective compounds have different effects compared to those of benzodiazepines. Chapter 2 demonstrated that TPA023 1.5 mg decreased saccadic peak velocity (SPV) comparably to lorazepam 2 mg. These results were similar for MK-0343 0.75 mg, as described in chapter 3, although this compound also produced small effects on the VAS alertness scale and on body sway. Chapter 4 showed that most measurements were not affected by SL65.1498, except for a decrease in SPV and smooth pursuit, which was for both effects smaller than decreases after lorazepam. The lack of or small effects on body sway, VAS alertness and memory could mean a more favourable side effect profile compared to the commonly used benzodiazepines. Zolpidem showed effects on most pharmacodynamic measurements, but not on memory, as described in chapter 5.

The meaning of the effects on the subjective VAS scales and body sway may be clear, but the exact meaning of the other CNS parameters still needs to be determined for this new drug class. These differential results suggest that a GABAergic decrease in SPV may primarily reflect the activity at the $\alpha_{2,3}$ subtypes, since this effect was relatively large for all $\alpha_{2,3}$ selective compounds.

The decrease in SPV despite a lack of subjective sedation that was shown by the three GABA_A $\alpha_{2,3}$ selective compounds was striking, and calls for a reconsideration of the meaning of SPV reduction particularly for this novel drug class. There can be little doubt that subjective sedation is accompanied by SPV reduction. It has on numerous occasions been shown to be closely related to the sedative effects of benzodiazepines and many other sedative agents and circumstances. However, the reverse –that SPV reduction always signifies subjective sedation – is not necessarily true. SPV reduction

has also been shown to be closely associated with the anxiolytic potencies of benzodiazepines [1]. Thus, benzodiazepine-induced SPV reduction may be caused by activation of both α_1 - and $\alpha_{2,3}$ -subtype receptors. For α_1 -selective hypnotics, SPV-reduction could be primarily due to their highly sedative properties. Other sedative compounds or conditions may cause SPV reductions without α_1 -activation, or through indirect stimulation of this part of the GABA-system. Subtype-selective $\alpha_{2,3}$ -activating compounds do not activate α_1 -subunits, and they do not cause subjective sedation through other mechanisms. For these drugs, SPV-reduction might be related to anxiolysis rather than sedation. Alternatively, the $\alpha_{2,3}$ receptor subtype may have direct effects on GABAergic neurons that are implemented in saccadic eye movements. In this case, sedation and α_1 -stimulation may have an indirect effect on these neurons, and α_2 - and/or α_3 -activation a direct effect. More preclinical and clinical studies with $\alpha_{2,3}$ selective compounds should be performed to confirm the hypothesis that SPV decreases are a more direct measure for $\alpha_{2,3}$ activity, and/or that they may be predictive for anxiolytic effects of this new drug class.

The studies that are described in chapter 2 to 4 each have contributed to the development of the compound concerned. In the first place, these studies helped to decide on dosing regimens. Additionally, these pharmacodynamic results provided information about the role of the different α -subtypes of the GABA_A receptor in these effects. The studies also confirmed that the drugs were pharmacologically selective in humans. This knowledge may be useful for future drug development of selective GABAergic drugs. The analysis of the different effect relationships that is described in chapter 7 was an attempt to determine the specificity of pharmacodynamic effects and evaluate their relation to the pharmacological characteristics of different selective compounds. In the discussion of this chapter, it is hypothesised that the level of efficacy at the α_1 subtype, which is known to be associated with sedation in animal models, is decisive in the development of sedation for this class of compounds. This thought was created as TPA023 and MK-0343 showed no or small efficacy at the α_1 subtype, as assessed by electrophysiological studies. They also seemed to be the most selective compounds with regard to the pharmacodynamic effects with no or hardly any sedative effects. Conversely, zolpidem, which has a high affinity for α_1 subtype receptors, caused relatively high levels of subjective sedation. Future research should confirm this hypothesis and reveal the significance and predictive value of these analyses for the therapeutic efficacy.

Despite its pharmacological selectivity, the pharmacodynamic effects of the α_1 -selective zolpidem showed a large overlap with the effects of benzodiazepines (chapter 5), although maximum effects seemed less. The effects on VAS alertness seemed to be relatively

large compared to those on SPV, although the difference in effect-relationship compared to lorazepam did not reach statistical significance (chapter 6). Since many CNS-effects heavily depend on attention and vigilance, sedation may indirectly affect most other CNS-parameters. Thus, even the most α_1 -selective compound is expected to secondarily influence other CNS-effects that are not directly affected by this receptor subtype. This could explain why zolpidem had a range of CNS-effect that would not have been expected to occur with α_1 -stimulation, such as reductions in body sway and SPV. Zolpidem did not affect memory (compatible with its lack of α_5 -efficacy), but tests of this cognitive function require active participation of the subjects, which may overcome limited impairments of alertness and attention. More passive tests like saccadic eye movements and postural stability may be more susceptible to sedation.

Thus, based on preclinical data and previous studies with benzodiazepines, several pharmacodynamic effects could be linked to certain GABA receptor subtypes. Sedation is believed to be associated with activation of the α_1 -receptor subtype. It could therefore be hypothesized that visual analogue scales of subjective alertness could reflect α_1 -receptor subtype activity [2-5]. The decreases in saccadic peak velocity could, as a result of sedation, also reflect activity of the α_1 -receptor subtype [6]. Body sway (postural instability) could have a potential association with α_1 -receptor subtypes, as a manifestation of sedation [7,8]. Memory effects could be related to α_5 -receptor subtypes [9-11], and is only affected by significant sedation that cannot be overcome with active participation. The results of the studies in section one suggest that $\alpha_{2,3}$ activity is also reflected by decreases in SPV and not by effects on body sway (as a possible result of muscle relaxation). These conjectures are summarized in figure 1, which shows a hypothesized model that represents the relations between GABA_A receptor subtypes, pharmacodynamic and clinical effects.

The knowledge about the relation between activation of certain GABA_A receptor subtypes and their related pharmacodynamic effects may be helpful in optimising the effect-profiles of this novel class of compounds. Additionally, relation of these pharmacodynamic effects to the therapeutic effects may in future possibly result in a biomarker for the anxiolytic effects.

The pharmacodynamic measurements have not only helped in the understanding of the effects of different GABA_A subtypes but have also been useful in the finding that zolpidem's effects quickly disappear, which may be caused by acute tolerance. Most PD measurements showed that a sigmoid E_{MAX} and a transit tolerance model could be used to describe the concentration effect-relationship. For both SPV and EEG alpha (Pz-Oz) power, low tolerance concentrations

were predicted, which indicated less tolerance than for the other parameters. The differential timescale of development for the behavioural parameters suggests that different benzodiazepine targets or different signalling processes may be involved in the development of tolerance for each of these parameters [12]. Although the underlying mechanisms are unknown, the acute tolerance might, besides the selectivity of the drug, also contribute to the short duration of action of this compound, which seems to be its major clinical benefit.

The α_1 subtype could play a role in the development of acute tolerance but also seemed to play a role in the development of pseudo-hallucinations, as described in chapter 6. These effects were seen in a subject after zolpidem intake. It was clear that all PD effects were more expressed in this subject, compared to those of other subjects. It was suggested that highly sensitive subjects may possess an over-expression of GABA receptor α_1 -subtypes or show a more rapid activation of GABA_A receptors after intake of a compound with a quick absorption. In both cases, an unbalanced activation of different GABAergic systems may have occurred, leading to hallucinations, comparable to hypnagogic hallucinations which can be viewed as a dissociation of sleep stages.

Although GABAergic drugs are widely used for different CNS-disorders, it is not always known why they are effective as often the exact pathophysiology is unknown. The use of novel GABAergic drugs in patient populations could be used to explore novel indications of the compound or to better understand the pathophysiology of the disorder, particularly the role of different GABAergic systems. In section two of this thesis, this potential use of different GABAergic or GABA-like drugs was investigated.

Chapter 8 showed that TPA023 showed similar CNS differentiating effects as seen in healthy volunteers were also found in (elderly) subjects with essential tremor (ET). However, no effects on tremor could be found. This suggests that the $\alpha_{2,3}$ subtype GABA_A receptor is not involved in the tremor reducing effects of benzodiazepines. This also suggests that this subtype is not involved in the pathophysiology of this disorder. Recently, the α_1 subunit knockout mouse has been introduced as an animal model for ET as it exhibits postural and kinetic tremors that clearly reproduce the features of essential tremors [13,14]. Therefore, our results seem to link with this recent finding. Also, these findings suggest that an α_1 -selective GABA-agonist would be needed to treat ET. A pilot study, however, demonstrated no correlations between variants in gene coding for this receptor subtype and ET patients [15]. Nevertheless, other defects in the α_1 subunit may still play a role in the pathophysiology of ET. Considering the (additional) role of the α_1 subunit in subjective sedation, it may be

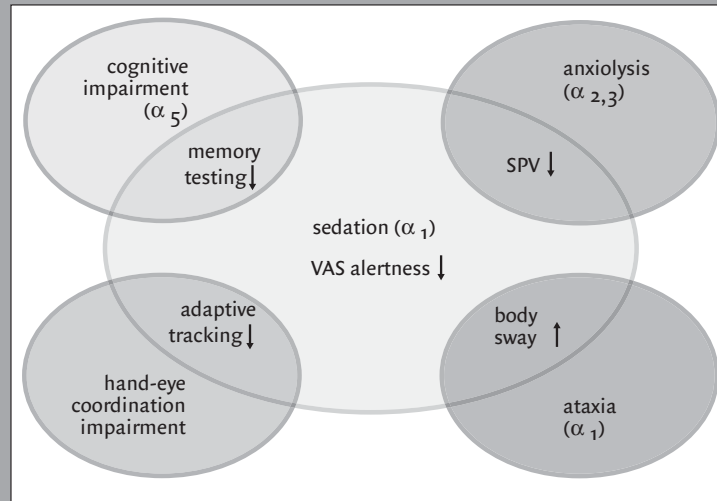
impossible to find a truly non-sedating GABAergic anti-tremor agent. Although sedation may be inevitable, this undesired effect may show a therapeutic window compared to the anti-tremor effect, which may be managed in practice with dose titration and tolerance development. There may also be other pharmacological mechanism to reduce tremor.

GABA-like drug have been used for many decades to treat epilepsy and sleep disorders. The development of a new GABA-like anti-epileptic gave rise to the question, whether this drug may also have beneficial effects on sleep. Chapter 9 showed that sleep disorders are more prevalent in epilepsy patients than in matched controls. The exploratory study that is described in chapter 10, suggests that pregabalin may improve sleep continuity in patients with partial epilepsy and clinically relevant sleep disturbance. The relationships between epilepsy and sleep disturbance are complex and hardly understood. However, it is not surprising that epilepsy and sleep disturbance both may benefit from a GABAergic compound. Although it is not known if the effect of pregabalin is a direct effect on sleep or an indirect effect due to improvement in sub-clinical or inter-ictal activity, these preliminary findings suggest that pregabalin may be an effective sleep-promoting drug in epilepsy patients.

The first section has shown that carefully designed studies in healthy volunteers, using a range of CNS-measurements that reflect different GABAergic systems aid in the development of new GABAergic drugs. Decreases in SPV seem to reflect activity at the $\alpha_{2,3}$ GABA receptor. Additionally, the efficacy level at the α_1 subtype seems to be decisive for the development of sedative effects. Section 2 showed that treatment with novel GABAergic drugs can help in understanding the role of GABAergic systems in certain disorders, and to identify new indications for this old drug class. It appeared that the $\alpha_{2,3}$ GABA receptor does not seem to play a role in the therapeutic effects of benzodiazepines on essential tremor, and that the GABA analogue pregabalin improves sleep continuity in patients with epilepsy and clinically relevant sleep disturbance.

Overall, this thesis has shown that pharmacodynamic measurements are useful in practically all stages of development of novel GABAergic drugs. The careful use of well-characterised selective pharmacological agents and pharmacodynamic methods may help to unravel the role of GABAergic systems in health and disease.

Figure 1 Diagram that shows the hypothesised relation between different clinical effects, pharmacodynamic measurements and GABA_A-receptor subtypes. SPV = Saccadic Peak Velocity



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