Chapter 7

The effects of apomorphine on visual perception in patients with Parkinson's disease and visual hallucinations; a pilot study

L. Geerligs[1,2], A. M. Meppelink[1,2], W. H. Brouwer[1], T. van Laar[1,2]

(1) Department of Neurology, University Medical Center Groningen, The Netherlands
(2) School of Behavioral and Cognitive Neurosciences, University of Groningen, the Netherlands

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7.1 Abstract

Visual hallucinations (VH) often occur in patients with advanced Parkinson's disease (PD). Overstimulation of dopamine receptors has been considered as one of the causes for VH in PD. However, several clinical studies suggested that apomorphine infusion did not worsen existing VH in PD, but could even improve VH in some PD patients. This pilot study included 4 PD patients with VH, who were examined before, during and after an intravenous infusion with apomorphine. The examinations included tests for lower and higher order visual functions, attention and motor functions. Apomorphine had a significantly positive effect on contrast sensitivity and showed a significantly negative effect on attention. These results may explain why apomorphine is able to improve VH in PD in some patients with mainly visual perceptive problems, but may also worsen VH in other patients, due to impaired attention.

7.2 Introduction

Visual hallucinations (VH) often occur in patients with advanced PD and are associated with problems on behavioural and functional level and higher mortality (Holroyd et al., 2001). Although overstimulation of dopamine receptors has frequently been suggested as the cause for VH in PD (Diederich et al., 2005), there is contrasting evidence. Several clinical studies showed that subcutaneous infusion of apomorphine did not worsen existing VH (Morgante et al., 2004; Di Rosa et al., 2003), whereas another study even suggested that apomorphine could improve VH in PD (Ellis et al., 1997). A recent clinical study from our center, using subcutaneous infusion of apomorphine in PD patients with VH, showed that equipotent conversion from oral dopamine agonists to subcutaneous apomorphine infusion was able to improve the frequency and severity of VH in PD (submitted). Other clinical studies in which apomorphine was administered in PD patients, showed an improvement of contrast sensitivity (Buttner et al., 2000), which may be related to the improvement of VH. This study aims to confirm this finding of the effect of apomorphine on contrast sensitivity and to broaden the scope by investigating the effect of apomorphine on various visual, cognitive and motor functions in PD patients with VH.

7.3 Patients and Methods

7.3.1 Design

All patients were examined three times during this study. The first time at baseline, while they were using their standard medication, the second time during steady state intravenous apomorphine infusion and the third time 2 hours after having stopped the infusion. All patients were on dopaminergic medication during testing. The following tests were used to analyse possible changes in vision, cognition, motor- and executive functions at the pre-infusion, infusion and post-infusion examinations.

Motor function: Unified Parkinson's Disease Rating Scale (UPDRS) part III

Lower order visual functions: (1) Contrast sensitivity measured in log units (Mars Letter Contrast Sensitivity Test); (2) Visual acuity (Snellen chart); (3)

Colour Discrimination (Farnsworth D-15; we used the Total Colour Difference Score (TCDS) in which a lower score indicates better colour perception) (Farnsworth and Society, 1947);

Higher order visual functions: Visual object and space perception battery (VOSP) (Warrington, 1991)

Attention: Reaction time with and without auditory cue corrected for motor times (Schuhfried S7, (Schufried and Mîdling, 1992)

Executive functions and cognition: (1) Frontal Assessment Battery (FAB) (Dubois et al., 2000); (2) Scales for Outcomes in Parkinson's disease, cognition (SCOPA-Cog) (Marinus et al., 2003)

Control task: Prosody test (Bos et al., 2005), because the performance on this task is expected not to change with apomorphine infusion.

The intravenous apomorphine infusion (30μg/kg/hr) lasted for 3 hours in total, after an initial bolus of 20μg/kg. All patients were pre-treated during 24 hours with 20 mg domperidon t.i.d., in order to prevent nausea and vomiting, which may be caused by apomorphine. One hour after the bolus injection and the infusion of apomorphine, a steady state plasma concentration was expected to be present. At that time the whole test battery was repeated. Two hours after having stopped the apomorphine infusion (4 times the elimination half-life of apomorphine (30 min), a selection of tests, not influenced by retest effects, were performed for the third time to control intra-individually for the effect during steady state infusion. Because of the short duration of the apomorphine infusion and the infrequent hallucinations in our patient group (which is usually the case in PD patients with VH) it was not possible to score the effects of the apomorphine on the VH.

7.3.2 Subjects

Four patients were selected according to the following in- and exclusion criteria.

Inclusion criteria: (1) Diagnosed Parkinson's disease according to the UK Brain Bank Criteria; (2) At least weekly hallucinations during the past month; (3) Mini Mental State Examination>24; (4) FAB>10; (5) Patients must be

able to understand the procedures; (6) Medication must be stable for at least one month.
Exclusion criteria: (1) Severe visual disorders (cataract, macula degeneration, severe retinal pathology, visual acuity$<$ 0.5); (2) Patients with cerebral electrodes for deep brain stimulation; (3) Presence of other neurological or psychiatric disorders; (4) Unstable internal disease.

All patients in this study had insight into their hallucinations and none of them had delusions. The levodopa equivalent dose of medication the patients were taking at the time of the study varied from 625 mg to 1950 mg (mean 1256). Three patients were on antipsychotic medication at the time of the study. Of these patients, one used clozapine (25 mg) and galantamine (24 mg), another used clozapine (25 mg) and rivastigmine (6 mg) and one used only rivastigmine (9 mg).

7.3.3 Statistics

To model the data, multilevel models for change were used. Multilevel modeling with repeated measures is preferable instead of analysis of variance procedures because fewer assumptions are made, which guarantees a more open analysis (Quene and van den Bergh, 2004). In the multilevel models, we used a random intercept parameter to model the pre-test data, since there were clear differences between patients in their pre-test scores. Because the effect of apomorphine was similar over all participants, no random slope parameter was added. Multilevel analysis can only estimate linear effects, whereas we were interested in quadratic effects over time; we expected a different score during apomorphine infusion compared to the pre- or post-test scores. Therefore two dummy variables were used in the analyses; both dummies used the pre-infusion measurement as the reference. The first dummy indicates whether there was a significant difference between the pre- and during infusion tests. The second dummy indicates whether there was a significant difference between the pre and post infusion measurements.

7.3.4 Ethics

This study was approved by the Medical Ethical Committee of the University Medical Centre Groningen. All participants signed an informed consent prior

to study inclusion.

7.4 Results

Apomorphine improved the contrast sensitivity during steady state infusion, as compared to the pre-test situation [t(8)=2,51; p=0,036]. While the mean scores on the pre- and post-tests were equal (1,55) [t(8)=-0,14; p=0,893], mean scores during the infusion increased with log 0,09. However, apomorphine did not show a significant effect on the UPDRS motor scores, on cognitive- and executive functions, and also not on visual acuity, colour perception and object and space perception (VOSP).
On the contrary the reaction times were significantly higher during apomorphine infusion, as compared to pre-test data [t(6)=4,20; p=0,006]. The mean reaction times on the pre- and post-test were 345 ms and 371 ms respectively, while the mean reaction time during infusion was 430 ms. The difference between the pre- and post-test were not significant [t(6)=1,29; p=0,244]. A similar result was found for reaction times with auditory cue, which showed a significant difference between the pre- and during-infusion tests [t(6)=2,83; p=0,030] and no difference between the pre- and post tests [t(6)=1,19; p=0,281].

7.5 Discussion

The main hypothesis of this study was that apomorphine infusion would increase both lower and higher order visual functions. This hypothesis was partially confirmed, because only contrast sensitivity improved significantly, but not colour perception, visual acuity or visual object and space perception. Deficits in contrast sensitivity have been shown to be larger in PD patients with VH compared to patients without VH (Diederich et al., 1998). While a positive effect of apomorphine on contrast sensitivity in PD patients has been shown earlier (Buttner et al., 2000), no study so far has examined the effect of apomorphine in PD patients with VH. Retest effects are unlikely to explain the differences with the interval of 3 months between measurement 1 and 2, because own data on file did not show any retest effects 3 months after baseline, in patients with PD and VH.
The UPDRS motor scores could be expected to improve with the infusion of apomorphine (Frankel et al., 1990). However, the UPDRS motor scores showed

a trend toward an increase instead of decrease during the infusion with apomorphine, as compared to the pre-test data. The scores during the infusion and at the post-infusion test were similar. The most likely explanation for this result is that we were looking at a ceiling effect, because the apomorphine was infused on top of the subjects' oral medication, which already relieved most of their motor symptoms. This suggests that apomorphine infusion in this study specifically influenced non-motor functions, i.e. attention and contrast sensitivity, independent of an effect on motor symptoms.
Apomorphine infusion increased reaction times, indicating a worsened attention. This finding is consistent with other data (Muller et al., 2002), indicating that apomorphine has a similar effect on attention in hallucinating and non-hallucinating PD patients. Apomorphine infusion did not improve or worsen any of the frontal and cognitive functions, which is also in accordance with previous data (Alegret et al., 2004). However, it might be the case that there is a positive effect on cognition, which could be masked by the decrease in attention.

Our results have to be interpreted with caution, because of the open design and the small group size, which however seems to be enough to show significant differences. On the other hand, patients were their own controls and did not know anything about the value of the possible outcomes of the tests. We also included a control test (prosody test) which did not show any difference, indicating that patients did not increase their effort during the infusion. Finally, no difference was found in the VOSP scores, while the VOSP is likely to be influenced by both the effort of the patient and expectations of the person administering the tests. It was expected that the scores on the VOSP would increase during infusion. However, no differences were found, suggesting absence of an effect of apomorphine on higher order visual functions, but also absence of placebo effects.

Our data fit nicely in the perception and attention deficit model, which suggests that VH may result from a combination of reduced perceptual input and lowered attention (Collerton et al., 2005). Apomorphine causes an increase of lower order visual perception and a decrease of attention, the two main factors causing VH according to this model. If an attention deficit is the main cause of VH in a patient, apomorphine will most likely increase the frequency of VH, as has been reported in the literature (Frankel et al., 1990). However, if the main cause of VH can be attributed to reduced perceptual input, apomorphine may reduce the frequency of VH, as has been reported previously as well, despite the negative effect on attention (Ellis et al., 1997). Our data suggest an impor-

tant mechanism by which apomorphine might act as an effective anti-psychotic in selected cases, consisting of the improvement of predominantly visual perceptive disorders. If severe attentional deficits are present as well, one should prescribe firstly a cholinesterase inhibitor, which may lead to improvement of the attentional performance and perhaps also of the VH. Once the attention (and/or VH) have improved, apomorphine can be reconsidered to control the existing motor fluctuations. Future studies should address this issue in more detail. Especially the interaction between cholinesterase inhibitors and apomorphine might be relevant for this group of PD patients with VH.