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Dihydroergotoxine mesylate for the treatment of sialorrhea in Parkinson's disease

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ABSTRACT

Background: Many patients with Parkinson's disease (PD) suffer from sialorrhea. Sialorrhea is often treated with anticholinergics and botulinum toxin, but some adverse effects have limited the use of these treatments. Dihydroergotoxine mesylate is an α-adrenergic blocking agents as well as some affinities to the dopaminergic and serotonin (5-HT) receptors. In the current study, we examine the safety and efficacy of dihydroergotoxine mesylate in PD patients.

Methods: This study consisted of 2 phases. The intervention was 2.5-mg oral dihydroergotoxine mesylate twice daily in both phases. The first phase is a three-week open-label single-arm trial (n = 10). The second phase was a six-week randomized controlled trials with a crossover design (n = 20). Efficacy was assessed using the United Parkinson's Disease Rating Scale (UPDRS) sialorrhrea subscore and Sialorrhea Clinical Scale for PD (SCS-PD).

Results: In the first phase, the UPDRS sialorrhea score was 3.5 ± 0.53 vs. 1.9 ± 0.57 prior to and after the treatment ($P = 0.004$). The SCS-PD score decreased from 15.8 ± 2.78 to 9.9 ± 3.00 after the treatment ($P = 0.005$). The response rate (defined by at least 30% reduction in SCS-PD score) was 60%. In the second phase of crossover trial, the UPDRS sialorrhea score was 3.00 ± 0.56 in placebo weeks vs. 2.00 ± 0.65 on dihydroergotoxine in dihydroergotoxine weeks ($P = 0.001$). The SCS-PD was 12.50 ± 2.84 and 9.25 ± 2.86 versus, respectively ($P < 0.001$). The response rate was 10% and 55%, respectively ($P = 0.003$). There were no significant adverse effects.

Conclusions: Dihydroergotoxine mesylate is safe and effective for sialorrhea in PD patients.

1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD), affecting 1% of adults 60 years of age or older worldwide [1]. In addition to motor deficits (e.g., bradykinesia, rigidity, tremors, and impairments in postural or gait), many PD patients have other non-motor symptoms, including sialorrhea (over-salivation). Estimated prevalence of sialorrhea in PD patients ranges from 32% to 74% [2,3]. Drooling, defined as an involuntary loss of saliva, is an embarrassing problem in patients with severe sialorrhea [2].

Many factors contribute to sialorrhea in PD patients [4–7]. First, the speed of salivary excretion may be increased in response to an irritation in the mouth, which may contribute to the excessive sialorrhea [4,8]. However, several recent studies indicated that PD patients with sialorrhea actually produce less saliva than healthy controls [9,10]. The second contributing factor to sialorrhea in PD patients is swallowing dysfunction [7,11]. Third, the use of certain drugs for PD, including clozapine and cholinesterase inhibitors, could increase salivary excretion and aggravate sialorrhea [3,7,9].

Both pharmaceutical and non-pharmaceutical treatments have been used to manage sialorrhea in PD patients. Non-pharmacological approaches include gum chewing, behavioral modification, radiotherapy, and surgical intervention [11–14]. Gum chewing and behavioral modifications could improve motor control of the masticatory and tongue muscles, along with improving the stooped posture of the lips,

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but there have been limited studies to support the efficacy of these interventions [11,13]. Radiation to the parotid and submandibular glands could reduce saliva production, but could produce several adverse effects, such as loss of taste and dry mouth [15,16]. For obvious reasons, surgery is reserved only for patients with extremely severe symptoms.

Pharmacological treatments for sialorrhea in PD patients include anticholinergics, adrenergic receptor agonists, and botulinum toxin (BoNT) of both serotypes A (BoNT-A) and B (BoNT-B). Anticholinergics could reduce the production of saliva, but are associated with drowsiness, confusion, and hallucinations [17]. Local administration of anticholinergic agents, e.g., sublingual atropine, glycopyrrolate, and ipratropium bromide spray, is associated with less adverse effects, but there is only limited evidence supporting the efficacy [14,18]. Adrenergic receptor agonists have also been used, but there are no current recommendations for their use to treat sialorrhea in PD patients because there are few relevant studies [4,17]. Local injection of BoNT into the major salivary glands is the most effective therapeutic option and is recommended by the Movement Disorder Society (MDS) [2,19].

In the current study, we examined the efficacy of dihydroergotoxine mesylate, a selective α-adrenergic blocking agent, for sialorrhea in PD patients. The first phase was a three-week open-label trial in 10 patients. The second phase was a six-week, randomized controlled trial with crossover design in 20 subjects.

2. Methods

2.1. Patient recruitment

This study was carried out at the Nanjing First Hospital Affiliated to Nanjing Medical University during a period from May 2017 to July 2017. Study subjects were recruited from the outpatient clinic. For inclusion, subjects must meet all following criteria: 1) ≥ 18 years of age; 2) diagnosis of idiopathic PD based on the United Kingdom PD Society Brain Bank criteria; 3) a sialorrhea score, using the United Parkinson's Disease Rating Scale (UPDRS) part II (item 6) at ≥3; 4) subjects (or caregivers) were willing to keep a diary in which sialorrhea was scored on a daily basis. The exclusion criteria included: 1) sialorrhea caused by factors other than PD; 2) known hypersensitivity to dihydroergotoxine mesylate; 3) BoNT treatment for drooling within the past three months; and 4) symptomatic bradycardia, severe postural hypotension, symptomatic coronary insufficiency, severe organic heart damage, severe hepatic/renal dysfunction, active psychosis, or pregnancy/lactation.

2.2. Study design

The current study consisted of 2 phases. The first phase was a three-week open-label single-arm trial. During the first week, baseline sialorrhea score was established. For the second and third weeks, subjects received dihydroergotoxine mesylate tablet (ISCHELIUM®) at a daily dose of 5.0 mg (divided into 2 doses, taken orally after meals). Both test drug and the matching placebo were provided by POLIFARMA, S. p.A., Italy.

The second phase of the study was a 6-week randomized, double-blinded, placebo-controlled, crossover trial. During the first week, a baseline sialorrhea score was established. During the second and third weeks, subjects randomly received either dihydroergotoxine mesylate (5.0 mg, divided into 2 doses) or placebo. Week 4 was the washout prior to crossover. During the fifth and sixth weeks, subjects were switched (Fig. 1).

The randomization sequence was generated by a statistician not otherwise involved in the current study using a standard computer randomization program. Test drug and placebo were coded by a pharmacist not otherwise involved in the trial. Both the patients and assessors were unaware of the treatment assignment.

2.3. Patient measurements

Upon enrollment, subjects underwent a complete history and physical examination, including assessment using the UPDRS as well as the Hoehn and Yahr staging system. UPDRS score was evaluated once a week throughout the study period. The patient or caregiver scored the extent of sialorrhea twice daily directly using SCS-PD throughout the study period. For each subject, the mean sialorrhea score was calculated over the last three days of the baseline week and at each treatment week, separately. In the first phase of the study, the primary outcome was the difference in mean SCS-PD between the 2 treatment arms. For the second phase of the study, the primary outcome was the difference in response rate between the 2 treatment arms. Response was defined as reduction of SCS-PD score by at least 30% [18]. Adverse events were assessed using a questionnaire after week 2 and 4, and upon the closing visit.

2.4. Statistical analysis

Data were analyzed on an intention-to-treat basis, and the last-observation-carried-forward method was used for missing data. A paired Wilcoxon ranks test was used to detect differences in mean UPDRS part II sialorrhea score, SCS-PD, and UPDRS III score between the 2 arms. The response rate was analyzed using a χ^2 test. Power analysis was not conducted since no previous studies reported the effects of dihydroergotoxine mesylate on sialorrhea. The sample size was arbitrarily set at 20. Statistical significance was set at $P < 0.05$ (2-sided). All statistical analyses were carried out using SPSS 22.0.

3. Results

3.1. Subjects

A total of 30 subjects were included in this study: 10 in the first phase and 20 in the second phase. Demographic information and baseline characteristics are illustrated in Tables 1 and 2. None of the patients were previously treated for sialorrhea. All subjects completed the study protocol.

3.2. Efficacy

In the first phase of the study, 60% (6/10) of the patients responded to dihydroergotoxine mesylate (SCS-PD score reduction by 30% or more). The UPDRS part II (item 6) sialorrhea score was 3.5 ± 0.53 and 1.9 ± 0.57 prior to and after the treatment ($P = 0.004$; Table 1). The SCS-PD was 15.8 ± 2.78 and 9.9 ± 3.00 prior to and after the treatment ($P = 0.005$). The UPDRS III score was 34.7 ± 9.27 at the baseline and 34.8 ± 9.74 after the treatment ($P = 0.655$).

In the second phase of crossover design, the response rate was 55% (11/20) to dihydroergotoxine mesylate vs. 10% (2/20) to the placebo ($P = 0.003$). Mean UPDRS part II sialorrhea score was 2.00 ± 0.65 on dihydroergotoxine vs 3.00 ± 0.56 on placebo ($P = 0.001$; Table 3). The SCS-PD was 9.25 ± 2.86 vs. 12.50 ± 2.84 ($P < 0.001$). Mean UPDRS part II sialorrhea score rating and SCS-PD score in the washout week (3.25 ± 0.55, 13.70 ± 3.13, respectively) did not significantly differ from the baseline (3.35 ± 0.49, 13.95 ± 3.05, respectively) ($P = 0.157$ and 0.197, respectively). The treatment sequence (i.e., placebo during weeks 2–3 vs. weeks 4–5) had no effect on the sialorrhea scores.

Mean UPDRS III score was 35.90 ± 11.79 in the dihydroergotoxine weeks and 35.90 ± 11.14 in the placebo weeks. The swallowing score rating, UPDRS item 19 (hypomimia score rating), or item 28 (stooped posture score rating) did not differ between the dihydroergotoxine and placebo weeks.

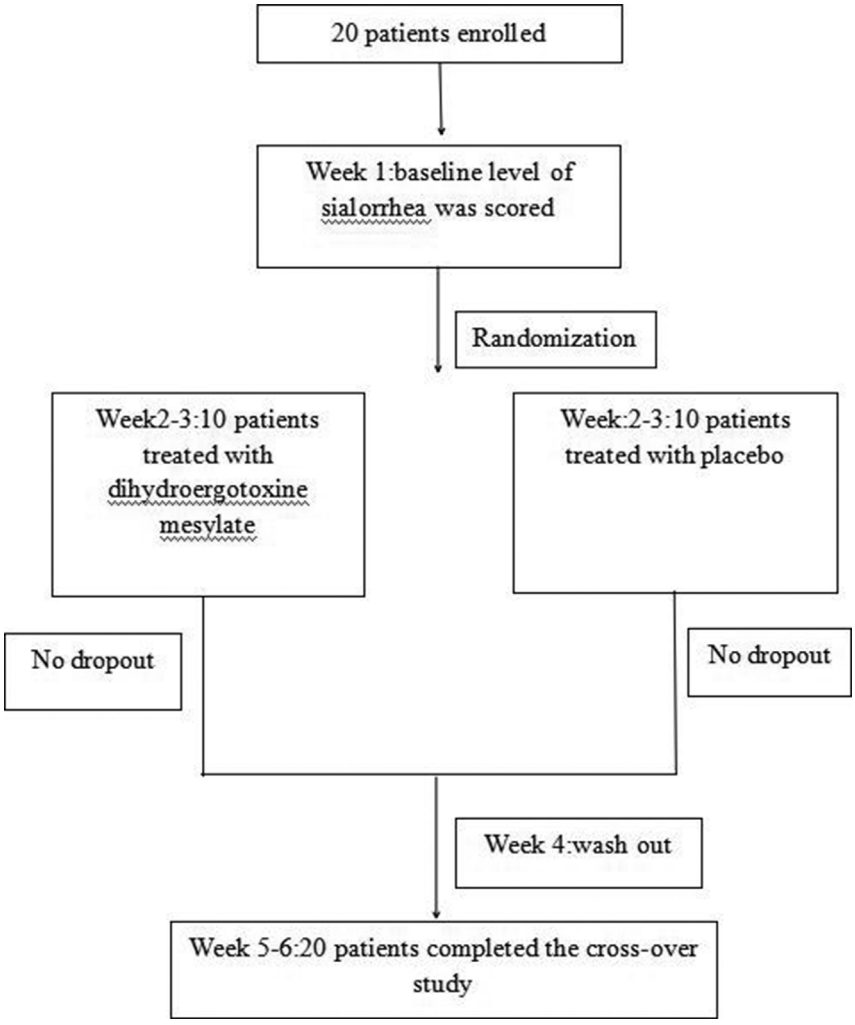

Fig. 1. Flow program of the study.

Table 1
Assessment at the baseline versus after the treatment in the first phase (n = 10).

Characteristics	Number of patients (n = 10)		
	Baseline	After treatment	*P* value[c]
Sex (M:F)	8:2	–	–
Age, mean (SD), years	72.9 (3.11)	–	–
PD duration, mean (SD), years	4.0 (2.75)	–	–
Hoehn and Yahr stage, mean (SD)	2.4 (0.74)	–	–
UPDRS part II, item 6[a], mean (SD)	3.5 (0.53)	1.9 (0.57)	0.004[d]
UPDRS part III, mean (SD)	34.7 (9.27)	34.8 (9.74)	0.655
SCS-PD[b], mean (SD)	15.8 (2.78)	9.9 (3.00)	0.005[d]

[a] UPDRS part II (item 6) is a sialorrhea score rating, with a range of 0–4.
[b] SCS-PD is a subjective assessment Sialorrhea Clinical Scale for Parkinson's disease, a higher score reflects more sialorrhea.
[c] *P*-value is calculated from a paired Wilcoxon ranks test between baseline and after treatment.
[d] Significant difference.

3.3. Safety

No serious adverse events were reported by either participants or caregivers in either the first or second phase of the study. In the first phase of the study, one subjects reported mild dry mouth, but the symptom dissipated three days later without intervention. Adverse events did not differ between the dihydroergotoxine and placebo weeks in the second phase (Table 3). All adverse events were temporary and dissipated without specific treatment.

Table 2
Demographic information and baseline characteristics of the patients in the second phase (n = 20).

Sex (M:F)	16:4
Age, mean (± SD), years	69.6 (9.53)
Duration of PD, mean (± SD), years	3.95 (2.44)
Hoehn and Yahr stage, mean (± SD)	3.0 (1.0)
UPDRS part II (item 6), mean (± SD)	3.35 (0.49)
UPDRS part III, mean (± SD)	36.75 (11.16)
SCS-PD, mean (± SD)	13.95 (3.05)

4. Discussion

The results from the current study showed that dihydroergotoxine mesylate could significantly attenuate sialorrhea in PD patients. The effects were evident in both objective and subjective measures for sialorrhea. Subjective measures of sialorrhea in the current study included SCS-PD and UPDRS part II (item 6) sialorrhea score ratings. The latter was used for screening, while SCS-PD was developed to investigate social and functional impairments with respect to the severity and frequency of drooling [20].

The percentage of patients who responded to dihydroergotoxine mesylate was 5.5-times higher than in the placebo. Specifically, 11 of the patients experienced an improvement in SCS-PD of 30% or more,

Table 3
Efficacy and adverse events of dihydroergotoxine mesylate.

	Dihydroergotoxine mesylate (n = 20)	Placebo (n = 20)	*P*-value[d]
Primary outcome			
> 30% improvement in SCS-PD (%)	11 (55%)	2 (10%)	0.003[f]
Secondary outcome			
UPDRS II (item 6), mean (± SD)	2.00 (0.65)	3.00 (0.56)	0.001[f]
SCS-PD, mean (± SD)	9.25 (2.86)	12.50 (2.84)	< 0.001[f]
UPDRS III	35.90 (11.79)	35.90 (11.14)	0.949
UPDRS item 7[a]	1.05 (0.89)	1.05 (0.89)	1.000
UPDRS item 19[b]	2.50 (0.76)	2.60 (0.88)	0.157
UPDRS item 28[c]	2.25 (0.79)	2.25 (0.79)	1.000
Adverse effects			
Orthostatic hypotension	1 (5%)	1 (5%)	1.000
Dry mouth	2 (10%)	1 (5%)	0.553
Edema	1 (5%)	0 (0%)	0.317

[a] UPDRS item 7 is the swallowing dysfunction score rating, with a range of 0–4.
[b] UPDRS item 19 was a hypomimia score rating, with a range of 0–4.
[c] UPDRS item 28 was a stooped posture score rating, with a range of 0–4.
[d] Efficacy analysis: paired Wilcoxon rank test for continuous variables and exact binomial test for correlated proportions. Adverse effects: exact binomial test for correlated proportions.
[f] Significant difference.

providing substantial evidence for the therapeutic efficacy of dihydroergotoxine mesylate. SCS-PD also significantly decreased after dihydroergotoxine mesylate treatment when compared with the placebo and baseline values. Furthermore, score did not differ significantly among the baseline, washout, and placebo weeks. A few patients informed us of improvements in movement disorder while on dihydroergotoxine, but assessment with UPDRS-III did not reveal improvement in motor functions. The results from this study showed minimal adverse events, suggesting that dihydroergotoxine mesylate is superior to anticholinergics this regards.

The pharmacological basis of the observed action with dihydroergotoxine mesylate is not clear. Two mechanisms might have contributed to the apparent efficacy. First, in addition to blocking α-adrenergic receptors, dihydroergotoxine could also activate dopaminergic receptors [4,21–23]. As a result, attenuated sialorrhea could be secondary to improvements in movement disorders. Measures of swallowing dysfunction (item 7), hypomimia (item 19), and stooped posture (item 28) in the UPDRS, however, did not differ significantly between the dihydroergotoxine and placebo weeks. The second potential mechanism is reduced saliva production and secretion. Several previous studies showed that the α-adrenergic blocking drugs clonidine and modafinil could attenuate drooling in PD patients [17,24]. Dihydroergotoxine mesylate is a potent and selective α-adrenergic blocking drug [25,26], and therefore could also attenuate sialorrhrea by reducing saliva production.

The current study is a single-centre study with small sample size. Also, we did not examine the long-term efficacy. The results, although encouraging, must be considered preliminary, and should be verified with multi-centre trials with sufficient power and long-term follow-up.

Study approval

The study protocol was approved by the Human Subjects Research Ethics Board of Nanjing Medical University. Written informed consent was obtained from all participants.

Author contributions

YYT, YDZ, and YQC designed the study. YQC, NNG, HHZ, ZTS, NHC, QH, and LW conducted the research. YQC, NNG, and TJ wrote the paper and analyzed the data. All authors reviewed and approved the final version of the manuscript.

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References

[1] B.S. Connolly, A.E. Lang, Pharmacological treatment of Parkinson disease, J. Am. Med. Assoc. 311 (2014) 1670–1683.
[2] J.G. Kalf, B.J.M. Swart, G.F. Borm, B.R. Bloem, M. Munneke, Prevalence and definition of drooling in Parkinson's disease: a systematic review, J. Neurol. 256 (2009) 1391–1396.
[3] R. Ou, X. Guo, Q. Wei, B. Cao, J. Yang, W. Song, N. Shao, B. Zhao, X. Chen, H. Shang, Prevalence and clinical correlates of drooling in Parkinson disease: a study on 518 Chinese patients, Park. Relat. Disord. 21 (2015) 211–215.
[4] P. Srivanitchapoom, S. Pandey, M. Hallett, Drooling in Parkinson's disease: a review, Park. Relat. Disord. 20 (2014) 1109–1118.
[5] A.C. Nóbrega, B. Rodrigues, A.C. Torres, R.D.A. Scarpel, C.A. Neves, A. Melo, Is drooling secondary to a swallowing disorder in patients with Parkinson's disease? Park. Relat. Disord. 14 (2008) 243–245.
[6] G. Umemoto, Y. Tsuboi, A. Kitashima, H. Furuya, T. Kikuta, Impaired food transportation in Parkinson's disease related to lingual bradykinesia, Dysphagia 26 (2011) 250–255.
[7] J.G. Kalf, B.R. Bloem, M. Munneke, Diurnal and nocturnal drooling in Parkinson's disease, J. Neurol. 259 (2012) 119–123.
[8] D.H. Nicaretta, A.L.Z. de Rosso, C. Maliska, M.M.B. Costa, Scintigraphic analysis of the parotid glands in patients with sialorrhea and Parkinson's disease, Park. Relat. Disord. 14 (2008) 338–341.
[9] J.G. Kalf, M. Munneke, L. van den Engel-Hoek, B.J. de Swart, G.F. Borm, B.R. Bloem, M.J. Zwarts, Pathophysiology of diurnal drooling in Parkinson's disease, Mov. Disord. 26 (2011) 1670–1676.
[10] O.R. Tumilasci, M.G. Cersósimo, J.E. Belforte, F.E. Micheli, E.E. Benarroch, J.H. Pazo, Quantitative study of salivary secretion in Parkinson's disease, Mov. Disord. 21 (2006) 660–667.
[11] A.R. South, S.M. Somers, M.S. Jog, Gum chewing improves swallow frequency and latency in Parkinson patients: a preliminary study, Neurology 74 (2010) 1198–1202.
[12] L.S. Eiland, Glycopyrrolate for chronic drooling in children, Clin. Therapeut. 34 (2012) 735–742.
[13] M.S. Troche, A.E. Brandimore, K.D. Foote, M.S. Okun, Swallowing and deep brain stimulation in Parkinson's disease: a systematic review, Park. Relat. Disord. 19 (2013) 783–788.
[14] T.R. Thomsen, W.R. Galpern, A. Asante, T. Arenovich, S.H. Fox, Ipratropium bromide spray as treatment for sialorrhea in Parkinson's disease, Mov. Disord. 22 (2007) 2268–2273.
[15] N.M. Hawkey, N.G. Zaorsky, T.J. Galloway, The role of radiation therapy in the management of sialorrhea: a systematic review, Laryngoscope 126 (2016) 80–85.
[16] A. Postma, M. Heesters, T. van Laar, Radiotherapy to the salivary glands as treatment of sialorrhea in patients with parkinsonism, Mov. Disord. 22 (2007) 2430–2435.
[17] K.L. Chou, M. Evatt, V. Hinson, K. Kompoliti, Sialorrhea in Parkinson's disease: a review, Mov. Disord. 22 (2007) 2306–2313.
[18] M.E. Arbouw, K.L. Movig, M. Koopmann, P.J. Poels, H.J. Guchelaar, T.C. Egberts, C. Neef, J.P. ven Vuht, Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial, Neurology 74 (2010) 1203–1207.
[19] K. Seppi, D. Weintraub, M. Coelho, S. Perez-Lloret, S.H. Fox, R. Katzenschlager, E.M. Hametner, W. Poewe, O. Rascol, C.G. Goetz, C. Sampaio, The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease, Mov. Disord. 26 (Suppl 3) (2011) S42–S80.
[20] S. Perez Lloret, G. Pirán Arce, M. Rossi, M.L. Caivano Nemet, P. Salsamendi, M. Merello, Validation of a new scale for the evaluation of sialorrhea in patients with Parkinson's disease, Mov. Disord. 22 (2007) 107–111.
[21] I. Setnikar, K. Schmid, L.C. Rovati, B. Vens-Cappell, D. Mazur, I. Kozak, Bioavailability and pharmacokinetic profile of dihydroergotoxine from a tablet and from an oral solution formulation, Arzneim. Forsch. 51 (2001) 2–6.
[22] A. Imperato, M.C. Obinu, L. Dazzi, G. Carta, M.S. Mascia, M.A. Casu, G.L. Gessa, Co-dergocrine (Hydergine) regulates striatal and hippocampal acetylcholine release through D2 receptors, Neuroreport 5 (1994) 674–676.
[23] A.N. Wadworth, P. Chrisp, Co-dergocrine mesylate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in age-related cognitive decline, Drugs Aging 2 (1992) 153–173.
[24] M. Serrano-Duenas, Treatment of sialorrhea in Parkinson's disease patients with clonidine. Double-blind, comparative study with placebo, Neurologia 18 (2003) 2–6.
[25] R. Markstein, A. Closse, W. Frick, Interaction of ergot alkaloids and their combination (co-dergocrine) with alpha-adrenoceptors in the CNS, Eur. J. Pharmacol. 93 (1983) 159–168.
[26] E. Müller-Schweinitzer, Actions of co-dergocrine mesylate and its components at vascular smooth muscle, Naunyn-Schmiedeberg's Arch. Pharmacol. 318 (1982) 225–233.