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Short communication

Bimodal dose-dependent effect on autonomic, cardiac control after oral administration of Atropa belladonna

Henrik Bettermann, PHD; Dirk Cysarz BSC; Andreas Portsteffen, PHD;
Hans Christoph Kümmell, MD

Department of Clinical Research, Gemeinschaftskrankenhaus, 58313 Herdecke, Germany

Address for correspondence:

Dr. Henrik Bettermann, Department of Clinical Research, Gemeinschaftskrankenhaus , 58313 Herdecke, Germany, Tel. +49 2330 62-3316, Fax +49 2330 62-4061,
Email hbetter@scientific-african.de

Abstract

This single-blind placebo controlled study was designed to investigate the dose-dependent vagolytic and vagotonic effects after a single oral administration of *Atropa belladonna* tincture (ABT, 0.1 mg/ml alkaloid concentration, atropine:scopolamine = 20:1). In 8 healthy young subjects, heart rate and noninvasive arterial finger blood pressure were recorded simultaneously over 4 h after oral application of 4 different doses of ABT (day 1: 2 ml, day 2: placebo, day 3: 5 ml, day 4: 1 ml). On each day, 14 20-min sequences under controlled experimental conditions were performed. Among others, mean RR interval (RR), high frequency spectral power of heart rate variability (HF), and noninvasive baroreflex sensitivity (BRS) were calculated during metronome breathing in supine position. These parameters were robust markers of vagal activity. One hour after 5ml ABT, RR, HF and BRS decreased clearly in 6 of 8 subjects. This effect was interpreted as vagolytic response. After 1 and 2ml ABT, and after placebo, RR and HF increased markedly. The increase after ABT was much higher than the increase solely due to adaptation after placebo administration, and it could be clearly identified as an augmentation of vagal cardiac activity caused by low-dose ABT. In conclusion, low doses of orally administered ABT can be effectively used to stimulate parasympathetic activity in man. The mode of vagal activation changes between 2 and 5 ml ABT from vagotonic to vagolytic. ABT has no or very little effect on blood pressure control.

Keywords: Heart rate variability, Atropine, Scopolamine, Spectral analysis, Herbal medicine, Beat-to-beat blood pressure, Baroreflex sensitivity

1. Introduction

Since the beginning of the 20th century, the bimodal effect of the belladonna alkaloids atropine and scopolamine on heart rate is well known (Wilson, 1916; Mc Guigan, 1921; Weiner 1985), and recently developed techniques for spectral analysis of heart rate variability (HRV) enabled deep insights into the dose-dependent effects of atropine and scopolamine on autonomic cardiac control (Montano et al., 1998). Low doses of both alkaloids significantly reduce heart rate and increase respiratory sinus arrhythmia (RSA), which is a marker of vagal cardiac control, whereas doses above ~5 µg/kg i.v. atropine and above ~3 µg/kg i.v. scopolamine markedly increase heart rate and decrease RSA. In clinical and experimental practice, particularly high or moderate doses of atropine are widely used to induce vagal blockade. Dose-dependent effects of atropine on autonomic cardiac control in healthy subjects have been investigated extensively in pharmacological studies (Alcalay et al., 1991, 1992; Das et al., 1975; Dauchot & Gravenstein, 1971; Julu & Hondo, 1992; Weise et al., 1989). Similar studies on the dose-dependent effects of scopolamine are rare (Bagshaw et al., 1970; List & Gravenstein, 1965; Redderson & Gravenstein, 1966). However, therapeutical effects of low doses transdermal scopolamine on cardiac function have been investigated comprehensively after myocardial infarction (Pedretti et al., 1993; De Ferrari et al., 1993; Vybiral et al., 1993; Casadei et al., 1993), in chronic heart failure (Casadei et al., 1996), in advanced congestive heart failure (La Rovere et al., 1994), in mild essential hypertension (Vesalainen et al., 1998), and in healthy subjects (Vesalainen et al., 1997; Vybiral et al., 1990). In all these studies scopolamine patches were used to administer a total dose of 0.5 mg scopolamine slowly and constantly within 24 to 72 h. As far as we know, therapeutical effects of low doses atropine have not been subject of investigation so far.

Objective of this single-blind placebo controlled study was to investigate the dose-dependent vagolytic and vagotonic effects after oral administration of *Atropa belladonna* tincture (ABT, Tinctura Belladonnae Normata DAB 10, 2. Nachtrag 1993, from *A. belladonna* leaves, Chemische Fabrik Dr. Hetterich, Germany), which is adjusted to a 0.1 mg/ml alkaloid concentration combined with a naturally given atropine/scopolamine ratio of 20:1.

2. Methods

In 8 healthy subjects (age 29.2 ± 8.2 years, four men) heart rate (Oxford Medilog FD3) and noninvasive arterial finger blood pressure (TNO Portapres II) were recorded simultaneously over 4 h after a single oral application of 4 different doses of ABT:

dose 1: 2 ml dose 2: placebo dose 3: 5 ml dose 4: 1 ml

The time between consecutive doses was at least 48 h. Fourteen 20-min sequences under controlled conditions (experimental sequences, ES) were performed with each dose. Each sequence consisted of 2.3 min of 0.2 Hz-metronome breathing in supine position followed by a 1-min period of active standing and a 16-min period of rest in supine position (see Fig. 1). The doses were administered in 0.2 l apple juice between the first two sequences. The subjects did not know which dose was given. All subjects gave their informed written consent. The protocol was approved by the ethics committee of the University of Witten/Herdecke.

As we intended to quantify vagal heart rate control, only heart rate parameters which are commonly attributed to parasympathetic activity were taken into consideration and were derived from Holter monitoring and from Portapres recordings:

- mean RR interval (RR),
- spontaneous baroreflex sensitivity (BRS),
- high frequency heart rate variability in the respiratory range (HF),
- 30:15 ratio of heart rate after standing up.

Other parameters like the low frequency power of heart rate variability (LF), the sympathovagal balance (LF/HF) or measures from nonlinear dynamics or information theory, were disregarded because of their sympathetically driven components. Except for the 30:15 ratio, all parameters were calculated for metronome breathing periods only.

According to Parlow et al. (1995) 'the spontaneous baroreflex method provides a reliable, non-invasive assessment of human *vagal* cardiac baroreflex sensitivity'. In this study the sequence method was used to quantify BRS in the time domain. The method is based on a technique originally introduced by Bertinieri et al. (1985) and selects all episodes of 3 successive heartbeats, which are characterized by a parallel increase or decrease of RR interval length and systolic blood pressure. From all these 'BRS sequences', the regression coefficients are derived and averaged over the period under consideration. Additionally the percentage of BRS sequences of all 3-beat-episodes (BRS%) is determined according to Malberg et al. (1999).

HF was computed using a straightforward FFT-based algorithm (see for example Rottmann et al., 1990). In short, this algorithm works as follows: after applying an ectopic beat filter (rarely necessary in the present data), which inserts, merges, averages, or smoothes certain misplaced R triggers, the RR tachogram is Parzen-windowed, resampled and Fast Fourier transformed. The resulting spectral power density function is integrated in the high frequency band between 0.15 and 0.25 Hz, and thus centered around the metronome frequency. HF power is expressed in milliseconds (by extracting the square root) such that its value corresponds to the standard deviation of the HF band-passed RR tachogram.

Furthermore, the heart rate response to standing up quickly from supine position was measured by calculating the so-called 30:15 ratio, i.e. the ratio of the longest RR interval around the thirtieth beat after standing up to the shortest RR interval around the fifteenth beat (see for example Ewing, 1988).

All computations resulted in discrete time series consisting of 14 values for each parameter and for each day of experiment. The time series were then characterized numerically by the parameter's relative increase during the first 2 h (INC, as a marker for a vagotonic effect, i.e. an increased vagal activity) or the parameter's relative decrease from the first maximum after oral administration of ABT to the following minimum (DEC, as a marker for a vagolytic effect, i.e. decreased vagal activity).

3. Results

In Table 1, the dose-response parameters INC and DEC with respect to RR, HF and BRS during metronome breathing are shown in percent. As an example, the dose-response curves for one subject are plotted in Fig. 2. It turned out that in our study, particularly, these parameters are robust markers of vagal activity.

After administration of 5 ml ABT the parameters HF, RR and BRS markedly decreased in most subjects after an initial augmentation; i.e. DEC(HF) was largest in all 8 subjects,

DEC(RR) was largest in 6 subjects, and DEC(BRS) was largest in 5 subjects in comparison to other doses. Altogether, consulting also the corresponding dose-response curves by visual examination, concordant vagolytic effects were evident in at least 6 of 8 subjects. The onset of these effects was approximately 1 h after administration, they were maximal after 2 h, and vanished after 4 h (see upper right diagrams in Fig.2).

The lower doses 1 and 2 ml ABT (and also the placebo) produced no concordant vagolytic effects, but increased clearly RR and HF during the first 2 h after administration, as an indication for vagal activation; i.e. INC(RR) was largest in 5 subjects after 2 ml, in 2 subjects after 1 ml, and in one subjects after 5 ml ABT. INC(HF) was largest in 3 subjects after 2 ml, in 4 subjects after 1 ml, and in one subjects after 5 ml ABT. In all but one case, the initial increases of both RR and HF were the lowest after placebo administration. The latter might be the most important finding as discussed below.

All other parameters, like the 30:15 ratio, BRS, BRS%, systolic and diastolic arterial finger blood pressure indicated no systematic effects which could be attributed to an enhancement of vagal activity.

After the application of the doses of 2 and 5 ml, slight mouth dryness was noted.

4. Discussion

In recent years, low-dose atropine and low-dose scopolamine have been proposed as centrally acting agents to enhance parasympathetic efferent activity. The positive influences on several diseases, for example on hypertension, were discussed only for low-dose scopolamine (see references above). In most studies low-dose atropine was given intravenously, and low-dose scopolamine was transmitted transdermally. Dose-dependent effects of oral administered atropine on cardiac autonomic control have been reported by Murrin (1973), Mirakhur (1978), Seppala & Visakorpi (1983), Miller & Friesen (1988), Chaudari et al. (1989) and others. As far as we know, oral applications of low-dose atropine have never been investigated.

A. belladonna tincture, as a naturally given composition, possibly combines the effects of both atropine and scopolamine. Moreover, Mazzanti et al. (1988) compared *A. belladonna* tincture with atropine for its anticholinergic activity, both in vivo and in vitro. “In all tests, the biological activity of *A. belladonna* resulted greater than that suggested by its alkaloid content. The results suggest the presence in *A. belladonna* leaves of unknown compounds with a significant biological activity.” (Mazzanti et al., 1988)

In this study, we tried to find the oral ABT dosage for which the vagal modulation changes from vagotonic to vagolytic. As a basis, we chose the range from 1 to 5ml ABT which corresponds to an alkaloid concentration of 0.1–0.5 mg, or approximately 1.35–8.62 µg/kg atropine, with respect to the range 58–74 kg body weight of the subjects in this study. This is the range for which bimodal effects of intravenous atropine have been demonstrated (Alcalay et al., 1992). The results of these studies served as guidance because similar data with respect to oral administration were too inconsistent (see references above) and could not be used for a reliable basic dosage estimation.

The results of the study confirmed that we were right with this decision: In 6 of 8 subjects, the 5 ml ABT dose resulted in a clear reduction of vagal activity, indicated by decreased RR and HF values, whereas doses below or equal 2 ml ABT produced the opposite effect. In each subject, the initial increase after 1 and 2 ml ABT of RR and HF was higher, or at least approximately the same, than the increase solely due to adaptation after placebo administration,

and could thus be clearly identified as an augmentation of cardiac vagal activity caused by low-dose ABT. The dose-response curves varied largely, although the experimental conditions were fixed as good as possible. The variations give rise to the presumption that many other factors than body weight or body mass index have an impact on the response to oral ABT. In this communication, it is not the place to speculate on the variety of factors, but it should be stated that there is a need to keep an eye on each individual response to ABT, and it cannot be assumed that large cross-sectional studies, e.g. on therapeutical effects of ABT, will produce homogeneous results. Probably, case studies are better suited to reflect subtle effects particularly after oral administration of compositions of herbal extracts.

In conclusion, low doses of orally administered *A. belladonna* tincture can be effectively used to stimulate parasympathetic activity in man. The mode of vagal activation changes between 2 and 5 ml single-dose ABT from vagotonic to vagolytic. ABT has no or very little effect on blood pressure control. Due to experimental design the comparison between oral administered atropine and ABT was not carried out in this study. Thus, the very interesting question, whether the herbal composition ABT is more effective than atropine alone, as assumed in literature, still remains unanswered.

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Fig. 1 Day of experiment: 14 experimental sequences of approximately 4 min duration were performed within 4 h after a single dosage of ABT or placebo

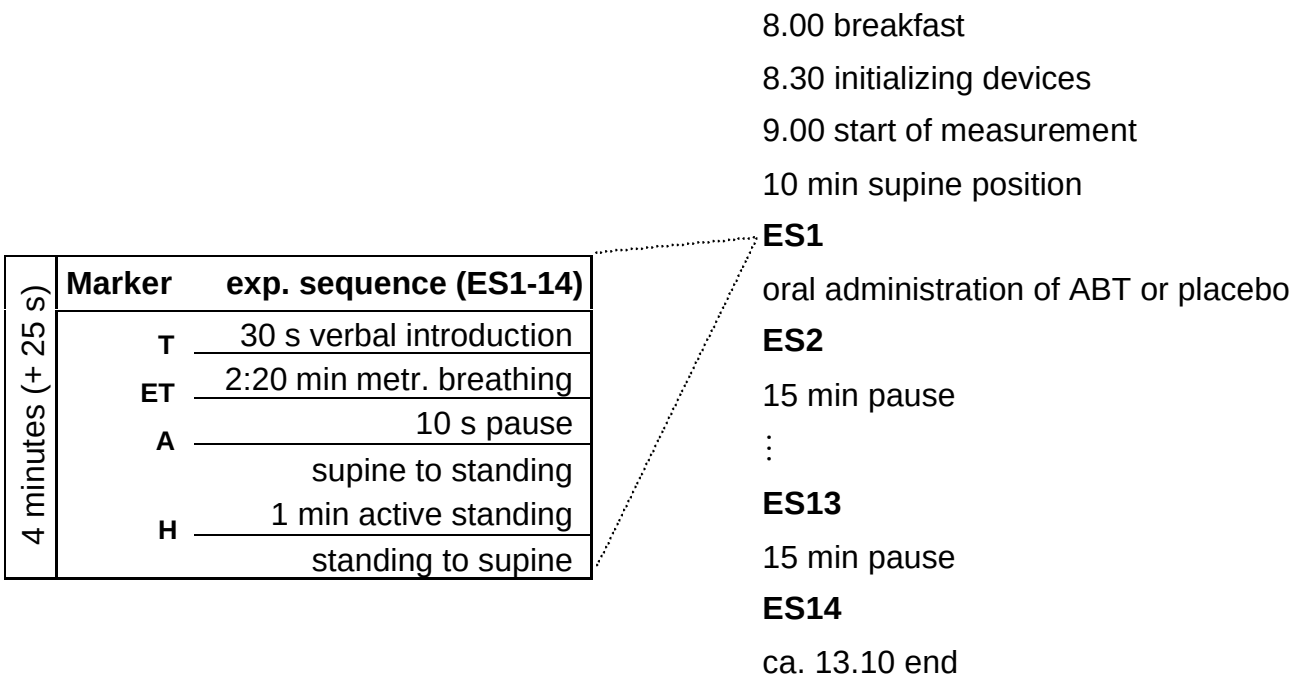

Fig. 2 Example: Time course of RR and HF during metronome breathing in supine position; horizontal axis: time in minutes after start of measurement

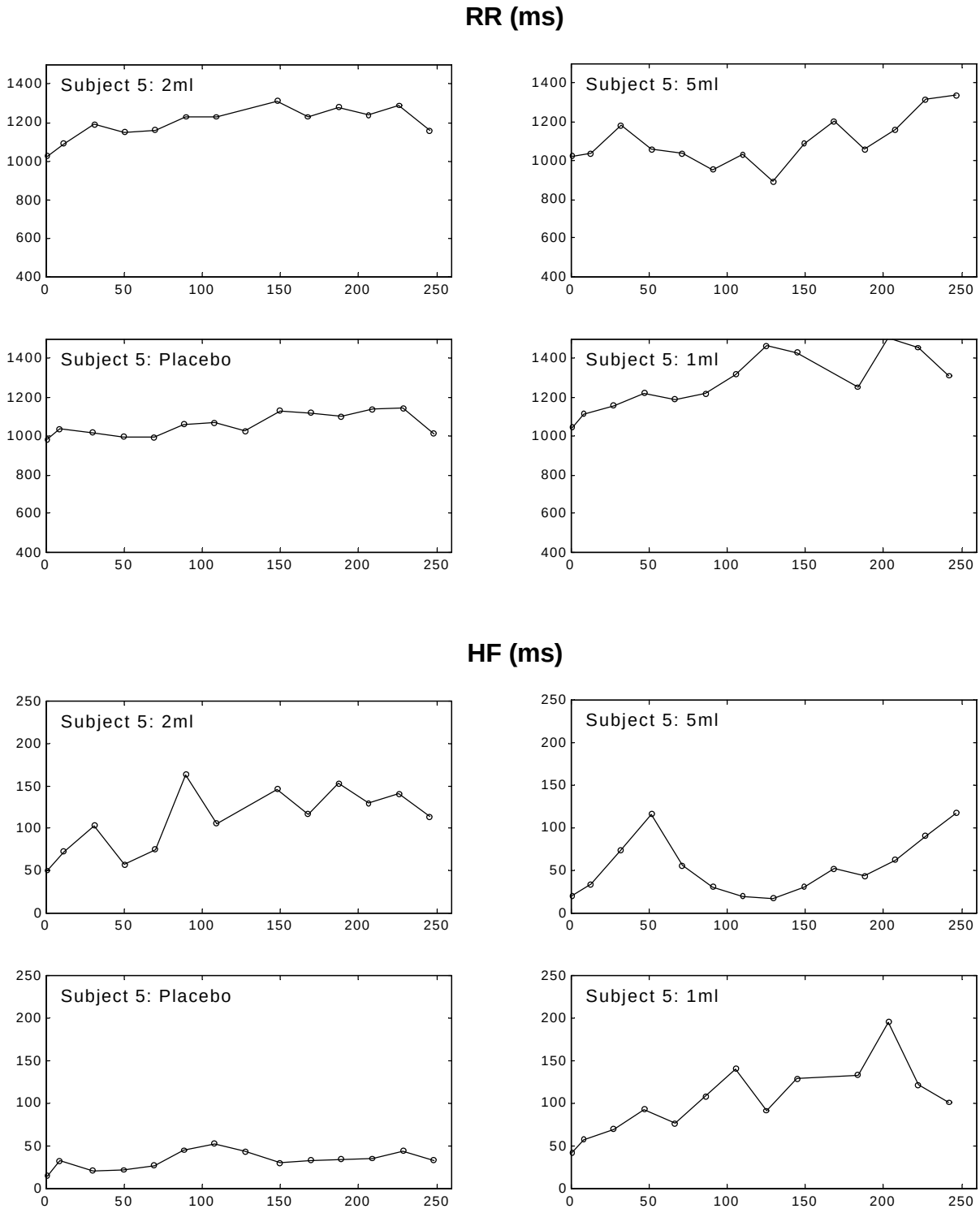

Table 1 Dose-response parameters INC and DEC in percent with respect to RR, HF and BRS during metronome breathing after 1ml (day 4), 2ml (day 1), 5ml (day 2) doses of ABT and after Placebo (P, day 3)

	INC(RR)				INC(HF)				INC(BRS)			
Subject	2ml	5ml	P	1ml	2ml	5ml	P	1ml	2ml	5ml	P	1ml
1	24	22	11	19	144	92	68	178	129	117	111	125
2	31	9	21	45	204	46	105	308	99	69	1	135
3	34	14	14	14	157	62	136	165	53	65	103	78
4	30	4	12	17	79	-50	5	1	82	-45	25	-6
5	16	8	6	22	93	119	49	130	67	82	43	27
6	28	-13	7	21	46	-50	8	15	14	-62	6	-9
7	16	0	0	6	134	19	-1	19	26	-27	-5	28
8	32	34	24	31	300	314	195	252	142	240	80	174

	DEC(RR)				DEC(HF)				DEC(BRS)			
Subject	2ml	5ml	P	1ml	2ml	5ml	P	1ml	2ml	5ml	P	1ml
1	7	11	9	6	28	72	10	0	58	46	55	31
2	20	11	20	6	34	75	34	14	41	55	46	39
3	11	11	3	8	40	59	0	31	45	56	14	30
4	15	24	13	21	58	85	23	46	51	67	36	74
5	6	25	5	5	35	85	43	35	34	80	46	43
6	0	51	13	2	33	99	14	28	33	95	66	51
7	1	22	1	4	38	89	38	9	22	74	22	44
8	8	7	5	8	40	61	38	22	60	57	39	38