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Efficacy of Homeopathically Potentized Antimony on Blood Coagulation

A Randomized Placebo Controlled Crossover Trial

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Key Words
Antimony · Anthroposophic medicine · Coagulation · Thrombelastography

Summary
Background: Homeopathically potentized antimony 6x is traditionally used in anthroposophic medicine for an alleged pro-coagulatory effect in bleeding disorders. However, the scientific evidence base is yet insufficient. Results of a previous in vitro study suggested a slight increase of maximal clot firmness (MCF) and a tendency towards a shorter clotting time (CT). The objective of this study was to investigate the pro-coagulatory effects of antimony in vivo, and possible unexpected or adverse events. **Participants and Methods:** A randomized placebo controlled double blind crossover study was carried out in 30 healthy volunteers (15 males, 15 females). Each participant received intravenously 10 ml of antimony 6x and placebo in a randomized order at an interval of 1 month. Thrombelastography (TEG) was carried out immediately before and 30 and 60 min after the injection. **Results:** Statistically significant pro-coagulatory effects were observed 30 min after injection for CT in men ($p = 0.0306$), and for MCF in men and women combined ($p = 0.0476$). The effect of antimony was significantly larger on test day 1 than on test day 2, whereas the effect of placebo was similar on both test days. No unexpected adverse or adverse events causally related to antimony were observed. **Conclusion:** This study adds evidence to the hypothesis that homeopathically potentized antimony may be efficacious in vivo. The consistency of the results with previous in vitro results indicates an effect on MCF and CT. The in vivo application of antimony 6x is safe.

Schlüsselwörter
Antimon · Stibium · Anthroposophische Medizin · Blutgerinnung · Thrombelastographie

Zusammenfassung
Hintergrund: Homöopathisch potenziertes Stibium D6 wird in der anthroposophischen Medizin traditionell wegen seiner angenommenen prokoagulatorischen Effekte eingesetzt. Die wissenschaftliche Evidenzbasis dafür ist noch ungenügend. Resultate einer früheren In-vitro-Studie deuten auf eine leichte Steigerung der Thrombusfestigkeit (MCF) und eine Tendenz zu kürzerer Gerinnungszeit (CT) hin. Das Ziel war die In-vivo-Untersuchung der prokoagulatorischen Effekte und möglicher Nebenwirkungen von Stibium. **Probanden und Methoden:** Im Rahmen einer randomisierten, placebokontrollierten, doppelblinden Crossoverstudie mit 30 gesunden Freiwilligen (15 Frauen, 15 Männer), erhielt jeder Proband intravenöse Injektionen von 10 ml Stibium D6 und Placebo in zufälliger Reihenfolge im Abstand von 1 Monat. Eine Thrombelastographie (TEG) wurde direkt vor der Injektion sowie 30 und 60 min danach durchgeführt. **Ergebnisse:** Signifikante prokoagulatorische Effekte wurden 30 min nach Injektion für CT bei Männern ($p = 0{,}0306$) sowie für MCF bei Männern und Frauen zusammen ($p = 0{,}0476$) gefunden. Der Effekt von Stibium D6 war am 1. Tag signifikant größer als am 2. Tag; wohingegen der Effekt von Placebo an beiden Tagen vergleichbar war. Es wurden keine mit Stibium verbundenen Nebenwirkungen beobachtet. **Schlussfolgerungen:** Diese Studie erhöht die Evidenz für die Hypothese, dass homöopathisch potenziertes Stibium in vivo wirksam sei. Die Übereinstimmung mit der früheren In-vitro-Studie weist auf einen Effekt auf MCF und CT hin. Die In-vivo-Anwendung von Stibium D6 ist sicher.

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Introduction

Antimony is traditionally used in anthroposophic medicine in a homeopathically potentized concentration to enhance homeostasis in a variety of bleeding disorders [1]. However, to date the scientific evidence base for this indication has remained insufficient. For this reason we had performed a placebo controlled in vitro pilot study, using freshly drawn citrate blood of 12 healthy donors and 12 patients with defined bleeding disorders. The results obtained by thrombelastography (TEG) were ambiguous as to whether antimony 5x had pro-coagulatory effects in vitro, although they indicated a small but statistically significant increase of maximal clot firmness (MCF) and possibly a shorter clotting time (CT) in the sample of healthy donors [1]. Based on these observations we have carried out a double-blind placebo controlled crossover in vivo trial to test the efficacy of antimony 6x in healthy volunteers. Commercially available antimony 6x in the most frequently used dosage in clinical practice to enhance hemostasis [2] and placebo, respectively, were administered, and parameters of TEG were measured. The main hypothesis was that antimony 6x has a pro-coagulatory effect in the sense of the previous in vitro study, i.e. enhances MCF and possibly shortens CT. Since a review of common practice as well as theory suggested that antimony is non-toxic in the doses usually applied [1], the second hypothesis was that the intravenous application of antimony has no adverse effects. Therefore, an assessment of possible adverse effects was performed by physically examining the participants and questioning them about changes in their health.

Participants and Methods

Participants

30 healthy volunteers (15 men, 15 women) were recruited by a poster distributed at the University of Bern. Inclusion criteria were: age 20–40 years, clinically healthy, no history or known risks of blood coagulation disorder, written informed consent. Exclusion criteria were: smoking, history of phlebitis, thrombosis, embolism, hypo- or hyper-coagulopathy, venous insufficiency, oral contraceptives, surgical intervention or anticoagulation within the last 3 months, intake of acetylsalicylic acid (ASA) or non-steroidal anti-rheumatic agents (NSAR) within the last week before and during the whole testing period, intolerance of ASA/NSAR or a history of gastrointestinal bleeding after its intake, and bearing a port-a-cath. The mean age was 26.8 years (20–38) for men and 29.3 years (21–37) for women. To optimize study compliance 150.– SFR were donated to the subjects upon completion of study participation. No dropouts occurred among the 30 volunteers.

Study Design

The study was carried out as a double blind placebo controlled crossover trial, according to the European standards of Good Clinical Practice (GCP) and the declaration of Helsinki. The protocol and the poster used for the recruitment of healthy subjects were approved by the Ethics Committee of the Canton of Bern (No. 130/30). Permission to carry out the study was obtained from SwissMedic, the Swiss Drug Administration, through a formal notification of antimony 6x. Written informed consent was obtained from all subjects prior to the measurements.

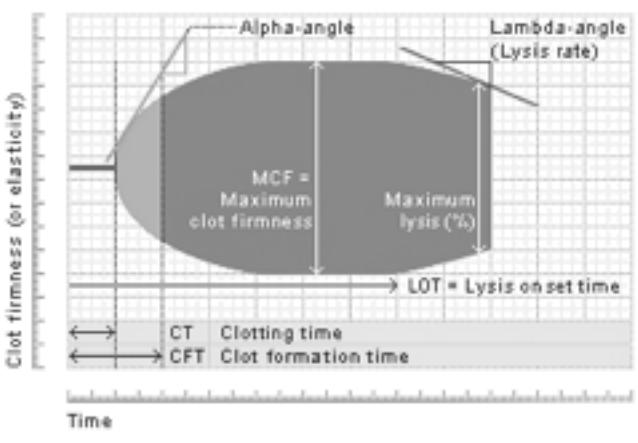

Fig. 1. Thrombelastographic recording of whole blood. CT is the time period from initiation of the measurement until the fibrin formation starts. CFT is the time period from the beginning of clot formation until an amplitude of the 20 mm is reached. MCF is the maximal amplitude of the TEG tracing. It is a function of the fibrinogen concentration, platelet count and their quality, and the interaction of fibrin and the platelet plug. Maximum lysis (ML) is representing the reduction of clot firmness during measurement due to fibrinolysis.

Test Substances and Randomization Procedure

Commercially available antimony 6x ('Stibium D6'; Weleda Inc.) and placebo (0.9% sodium chloride solution), ampoules of 10 ml each, were provided and submitted to the legally required quality control by Weleda Inc., Schwäbisch Gmünd, Germany. Placebo and antimony ampoules were externally indistinguishable. The ampoules were coded, labeled and packed in a computer-generated randomized order and then delivered to the Thrombosis Laboratory together with the corresponding randomization envelopes. These had to be drawn consecutively, according to the sequence of recruited subjects coming to their first test day. The randomization code remained at the Institute of Mathematical Statistics and Actuarial Science and was accessible only to the responsible statisticians.

Sampling Procedure and Laboratory Methods

Each participant received one intravenous injection of 10 ml antimony 6x and one intravenous injection of placebo at an interval of 1 month to exclude possible carry-over effects. The sequence in which antimony and placebo were given was randomized and double blinded, i.e. all subjects were seen on 2 different days (test day 1 and test day 2) and either received placebo on day 1 and antimony on day 2 or vice versa. Citrated blood samples were drawn immediately before as well as 30 and 60 min after both injections. Duplicates of each blood sample were immediately processed in parallel for analysis of coagulation by means of TEG as described earlier [1]. TEG permits to assess the entire coagulation process including fibrinolysis and detects activation of coagulation as well as enhanced bleeding. The parameters of clot formation and fibrinolysis determined by TEG are depicted in figure 1. The assay is performed on 300 µl of citrated whole blood that is placed in a preheated cup. The coagulation is initiated by adding 20 µl of calcium chloride solution at a concentration of 200 mmol/l. The runtime of this dynamic process is 60 min from the beginning of clot formation.

Endpoints for Testing Efficacy

For each subject, TEG parameters were measured and the differences between the values obtained immediately before (baseline) and 30 (D1) and 60 (D2) min after the injection were calculated. Furthermore, to test for differences of effects, the area A below the curve of measurements

Table 1. Numerical results for MCF in all subjects, and for CT in men, at D1, 30 min after injection of antimony or placebo; test day 1 and 2 refer to the two different days each subject was tested. Placebo → antimony refers to the group that received placebo on test day 1 and antimony on day 2, and vice versa.

Randomized groups	MCF (mm)		CT (s)	
	test day 1	test day 2	test day 1	test day 2
Placebo → antimony				
Mean	0.30	1.43	–51.43	–51.68
Median	–0.50	0.00	–21.75	–33.25
SD	2.57	3.89	173.00	76.06
Range	9.50	13.00	562.50	208.00
IQR	2.50	6.00	145.12	94.00
Antimony → placebo				
Mean	1.03	–0.64	–95.14	74.28
Median	1.25	–0.75	–91.00	–29.50
SD	1.32	2.23	62.21	205.87
Range	4.50	8.50	194.00	496.50
IQR	1.50	3.00	48.50	282.50

SD = Standard deviation; IQR = inter-quartile range.

at baseline, 30 min and 60 min was determined. While D1 and D2 show the response at a certain time point, the area is considered a measure of response of the whole treatment.

Safety: Assessment of Unexpected and Adverse Events

All subjects were explicitly asked about perceived changes in their health and were physically examined. Adverse events (UAE) were documented by an exact description and rated with respect to their intensity and causal relation to the tested substance (antimony or placebo). Intensity was rated as either 'mild', 'moderate' or 'serious'; and causal relation as either 'unrelated, 'unlikely', 'possible', 'probable' or 'definite', according to the generally applied Common Toxicity Criteria for Adverse Events [3].

Data Analysis

Based on the values for each test day the pre-post injection differences for all TEG parameters (post-injection minus pre-injection value, the pre-injection value considered as baseline) were calculated, D1 being the difference at 30 min, D2 the difference at 60 min, and A the area under the curve (A = D1 * 30 min + D2 * 30 min). Analysis was carried out for all participants and for genders. The latter was done because normal values of physiological and laboratory parameters tend to differ between genders. The three measures D1, D2 and A were analyzed with non-parametric methods for crossover studies based on ranks according to Brunner-Langer [4]. This approach was chosen because it is difficult to test for normality in small samples. Therefore it is more appropriate to apply non-parametric tests. The level of significance was set at $p \leq 0.05$ and no correction for multiple testing was applied, as this was an exploratory study. All computations were done with SAS V 9.1 and SPSS 13.0. The safety variables were listed descriptively in simple frequency tables (tables not shown).

Results

Efficacy

Statistically significant pro-coagulatory effects were observed in D1 (30 min after injection) for CT in men (p = 0.0306), and

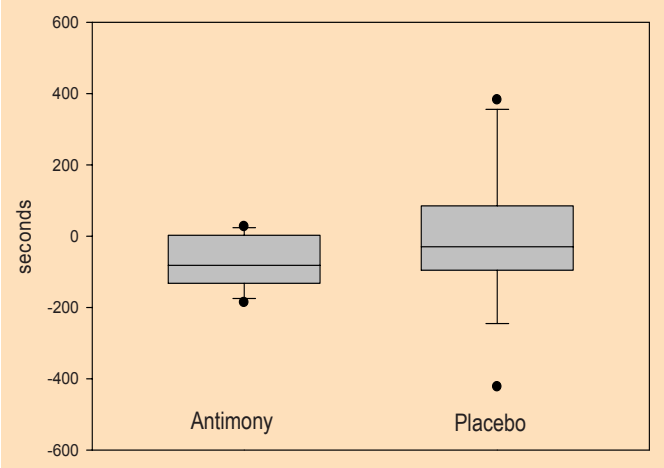

Fig. 2. CT differences D1 and their medians for antimony and placebo in men (p = 0.0306).

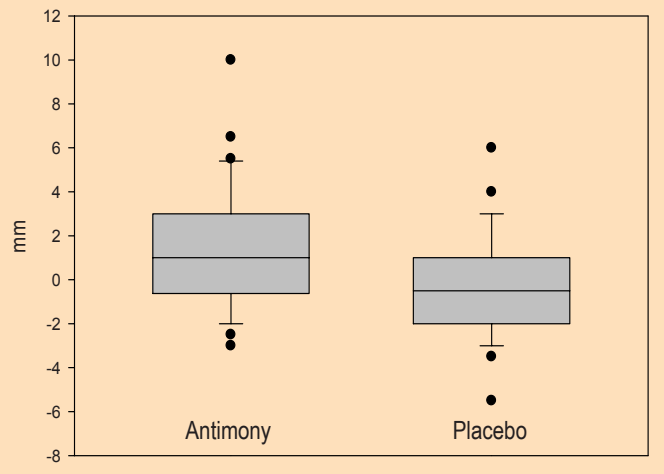

Fig. 3. MCF differences D1 and their medians for antimony and placebo in all subjects (p = 0.0476).

for MCF in men and women combined (p = 0.0476) (table 1). Figure 2 and 3 indicate the directions and the magnitudes of these differences in terms of individual values for CT and MCF. The results concur with the first hypothesis formulated in the introduction: In both men and women the median difference D1 for CT was more negative after antimony than after placebo, indicating a shorter CT with antimony than with placebo (fig. 2). Likewise, in both groups the median difference D1 for MCF shows higher values with antimony than with placebo, indicating a stronger clot formation with antimony than with placebo (fig. 3). The figures also show that quantitatively, the effect of antimony on CT and MCF was smaller than for the inter-individual variability. The effect of antimony was significantly different between test day 1 and test day 2, i.e. it was larger on test day 1 whereas the effect of placebo was almost the same on both test days.

Safety

None of the 30 subjects experienced any UAE judged as 'possibly', 'probably' or 'definitely' related to antimony or placebo. 5 subjects (2 men, 3 women) reported a total of five mild UAEs, 4 of them on test day 1, and all temporally related to the first blood sampling and the consecutive injection of the test substance (3 antimony, 2 placebo). A causal relation to the test substance was judged as 'unlikely' (3×) or 'unrelated' (2×). The reported sensations were transient pain, pressure or burning at the injection site or short-time dizziness that was interpreted as a parasympathetic reaction to the intravenous injection as such.

Discussion

The results of this study add some evidence to the hypothesis that homeopathically potentized antimony 6x has pro-coagulatory effects in humans in vivo.

Since this was an exploratory hypothesis-generating study, we did not apply a correction for multiple testing. A total of 36 tests were carried out. In principle, if a correction for multiple testing had been applied, none of the differences would have been significant. Thus, there is an elevated risk for a type I error. However, since these results are in agreement with the previous results of the in vitro study [1], a spurious significance seems unlikely. Still further studies are needed for confirmation.

Our results indicate pro-coagulatory effects of antimony by means of TEG. A statistically significant decrease of CT in men and an enhanced MCF in all participants after injection of antimony was found. These effects were detectable 30 min, but not 60 min after antimony injection. This is most probably due to the rapid distribution after the intravenous injection, a quick onset of its physiological effect and the short half life time of antimony.

The decrease in CT was only significant in men but a similar, though not significant trend was also observed in women.

The fact that not all thrombelastography parameters are altered by antimony is understandable because they are different parameters and are therefore likely to be influenced differently.

The question may arise whether the results may have been influenced by a carry-over effect. However, a carry-over effect can be excluded for three reasons. Firstly, the interval between the two test days was 4 weeks. Given the short half life time of antimony, a persisting antimony effect after 4 weeks is improbable. Secondly, we did not observe an antimony effect at 60 min after injection, which also corresponds to the short half life time and a quick wash-out of antimony. Thirdly, and most importantly, for each test day the differences for the TEG parameters before and after the injection were calculated. Therefore, even if there had been an antimony carry-over effect it would not have affected these calculations.

The TEG values show a broad distribution. This may be explained by (1) a technical error of measurement, (2) normal physiological variations or (3) effects of antimony. (1) The test-retest variability of the measurements of CT was 10.7% or 82.8 s and for MCF 2.9% or 1.4 mm. This effect accounts for a large part of the variability. To reduce this effect, duplicates of each blood sample were measured. (2) The variability due to physiological variation was similar in size. This may reflect genuine inter-individual differences in the response to antimony. In several studies it has been shown that herbal medication may be effective in patients affected by a certain disorder but not in healthy subjects. This may indicate that herbal and potentized medications rather have a regulatory than an imposing mode of action and therefore, an individually different reaction to antimony application may be conceivable. (3) The effect of antimony was approximately half as large as the test-retest variability and physiological variability. However, averaging across participants resulted in a reduction of test-retest and physiological variability. Therefore, the effect of antimony, which always went in the same direction, whereas test-retest variability and physiological variability did not, became visible.

The results of this study are in agreement with our previous in vitro study [1], in which we also found an enhancement of the coagulation parameters CT and MCF, for the latter statistically significant. The findings also correlate with in vitro experiments by Beck (unpublished data, reported in [1]) and the hypothesis formulated in the introduction on the basis of theory and retrospectively assessed clinical experience.

The effect of antimony was significantly larger on test day 1 than on test day 2, whereas the effect of placebo was almost the same on both test days. The reason for this remains yet unclear.

In summary, the consistency with our previous in vitro results and with the basic theory suggests that antimony has a mild pro-coagulatory effect. The fact that the effects were small may not necessarily mean a shortcoming, in particular from the perspective of safety. On the contrary, a large effect might have the disadvantage of being potentially dangerous such as leading to thrombosis, whereas this is highly unlikely in the case of effects within the range of physiological day-to-day variations as found in our experiment. But can such an effect still be of therapeutic significance? This may very well be the case. Healthy coagulation is an extremely flexible system that has to immediately counterbalance any deviation. For this reason an effect might be more difficult to detect in healthy persons than in patients with deviations from the normal equilibrium of coagulatory processes. From this point of view a weak pro-coagulatory effect apparent 30 min after administration of homeopathically potentized antimony may be an indication of a potentially valuable and, as apparent in our 30 volunteers, also safe remedy, worthy of further testing.

For this reason the next step of our investigation will be a randomized placebo controlled double-blind application of antimony 6x in patients with a clinical need of enhanced pro-coagulatory processes, e.g. in bleeding disorders.

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