Randomised, placebo-controlled, double blind clinical trial for the evaluation of the efficacy and safety of oral methanthelinium bromide (Vagantin®) in the treatment of focal hyperhidrosis

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Introduction

Hyperhidrosis is defined as excessive sweating [1]. A distinction is principally made between generalised and focal hyperhidrosis. Focal hyperhidrosis is generally idiopathic in nature, i.e. it is not possible to identify a trigger. Clinically, focal hyperhidrosis presents as drops of sweat developing, depending on the severity of the hyperhidrosis, in a matter of seconds and then becoming visible as sweat patches on the clothes. Subjectively, patients' experiences of focal sweating vary considerably. Some people who always have a sweat patch the size of the palm of a hand under their arms will not find this a problem, others may find it unpleasant but not in need of treatment, while yet others may find it extremely problematic and be ashamed of it or afraid that it will disadvantage them at work. Around 30% of patients demonstrate signs of social phobia [2].

Various options are available in the treatment of focal hyperhidrosis: aluminium chloride hexahydrate is the most significant of the local therapeutic agents; intracutaneous botulinum toxin A injections; tap water iontophoresis; oral anticholinergics such as bornaprine and methanthelinium bromide; and surgical procedures such as axillary suction curettage or transthoracic endoscopic sympathectomy.

Methanthelinium bromide is a quaternary ammonium derivative with anticholinergic effect. It differs from atropine in the predominance of blocking of ganglionic transmission over peripheral muscarinic transmission. Methanthelinium bromide reduces the muscle tone of the smooth muscles in the area of the gastrointestinal and urogenital tracts. It inhibits bronchial secretion, the secretion of saliva and sweat as well as the secretion of stomach acid. It also causes paralysis of accommodation.

The duration of effect of methanthelinium bromide following oral administration is clinically longer than that of atropine. For a therapeutic dose of 50–100 mg it is around 6 hours. Methanthelinium bromide has been commercially available to treat hyperhidrosis since 1951. Individual case reports have described the effect of methanthelinium bromide in treating hyperhidrosis [3, 4, 5, 6]. However, no clinically controlled studies to evaluate its efficacy have previously been carried out.

The aim of this double blind, placebo-controlled study was therefore to establish whether oral methanthelinium bromide treatment is able to suppress sweat production sufficiently in cases of focal hyperhidrosis.

Patients/Material and Methods

The study was carried out as a randomised, placebo-controlled, double blind clinical trial as part of the re-licensing process of the preparation, and was registered as such with the appropriate authorities. After ruling out any contraindications, serious concomitant illnesses or any interfering medication, patients aged 18–65 years who had been suffering from axillary and/or palmar hyperhidrosis for more than one year and who had previously been treated unsuccessfully with aluminium chloride hexahydrate and/or tap water iontophoresis were included in the study. The gravimetrically assessed sweat production had to be at least 50 mg/min for both axillae and/or hands.

Patients were randomised and then received treatment with either methanthelinium bromide or placebo coated tablets. The tablets had to be taken in the mornings and at lunchtime (one tablet

in the morning, one at lunchtime) at an interval of 6 hours. The total duration of treatment during the study was 4 weeks. The first control examination was carried out after patients had been taking the tablets for 2 weeks. The second control was carried out after 4 weeks, at the same time as the final examination. The primary target parameter was the reduction in the gravimetrically assessed sweat production to less than 50 mg/min while receiving treatment. Secondary target parameters were the absolute value of sweat production, the mean individual percentage reduction in sweat production, and differences in the frequency of adverse events. The quantitative measurement of the amount of sweat secreted was carried out by gravimetry. First, filter paper was weighed (1 x 4 coffee filter made by Melitta®). After drying the areas of skin to be measured with absorbent paper towels, the filter paper was secured under the axillae for one minute using plastic film[1]. The filter paper was then weighed again. To measure palmar sweat production the filter paper was laid out on a table and the patient then placed his/her palms onto this while standing, applying constant pressure. The difference in the weight of the filter paper was recorded as the amount of sweat produced in mg/min. A mean value was calculated for each location (axillae or hands) from the two values for the right and left side. Owing to pronounced variation in the gravimetric values, the values were collated (in the sense of repeat determination) at weeks –2 and 0 as "prior to treatment" and weeks 2 and 4 as "during treatment".

To assess the safety of the treatment, patients were questioned about adverse events and Schirmer's test was carried out to assess the effect of methanthelinium bromide on lacrimation.

The primary analysis was the intention-to-treat (ITT) analysis. The ITT population includes all randomised patients who used the test medication at least once, and for whom the target parameters were measured at least once after the initial findings at the beginning of the trial.

Statistical analysis was carried out using SAS®. The primary analyses were carried out using the Wilcoxon test for unconnected samples (comparison of the gravimeter values for methanthelinium bromide versus placebo before and during treatment) and for connected samples (comparison of the gravimeter values before and during treatment for methanthelinium bromide and placebo respectively). All tests were two-sided.

Results

A total of 41 patients were included in the ITT analysis. 23 had been randomised to the methanthelinium bromide group, 19 to the placebo group (see Figure 1). One patient withdrew his consent after being given the medication; for another patient the study was discontinued because Schirmer's test was pathological during treatment. The mean age in the methanthelinium bromide group was 25.2 ± 6.8 years (mean value ± standard deviation) (range 18.7 to 42.7), in the placebo group 31.5 ± 11.9 years (range 18.9 to 54.8) ($p = 0.04$, Wilcoxon test). In both arms of the study there were almost three times as many women as men. There were 18 women in the methanthelinium bromide arm (78%) and 13 women in the placebo arm (72%). There were therefore no differences in the distribution of the genders ($p = 0.72$, Fisher's exact test).

The methanthelinium bromide and placebo groups differed in the severity of the axillary hyperhidrosis. The patients who received methanthelinium bromide had significantly higher gravimeter values (89.21 ± 73.44 mg/min) before randomisation than the placebo patients (60.74 ± 42.83 mg/min) ($p = 0.06$, Wilcoxon Test). The values for the methanthelinium bromide group became close to those for the placebo group during treatment: the values for the methanthelinium bromide group were 53.3 ± 48.7 mg/min; for the placebo group the values were 59.1 ± 40.6 mg/min ($p = 0.48$, Wilcoxon Test) (see Figure 2 and Figure 3).

In the whole group the gravimetrically assessed sweat production reduced to less than 50 mg/min in 16 of the 23 methanthelinium bromide patients and 9 of the 18 placebo patients ($p = 0.21$, χ^2 test).

In the patient group who had axillary gravimeter values of ≥ 50 mg/min prior to treatment, 12 of the 18 patients in the methanthelinium bromide group and 2 of the 9 patients in the placebo group showed a reduction in the gravimeter value to <50 mg/min. This difference was significant with a p-value of 0.02 (χ^2 test, two-sided).

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[1] Translator's note: the German term 'Plastikrolle' is ambiguous here and could mean either 'plastic film' or 'plastic roller'.

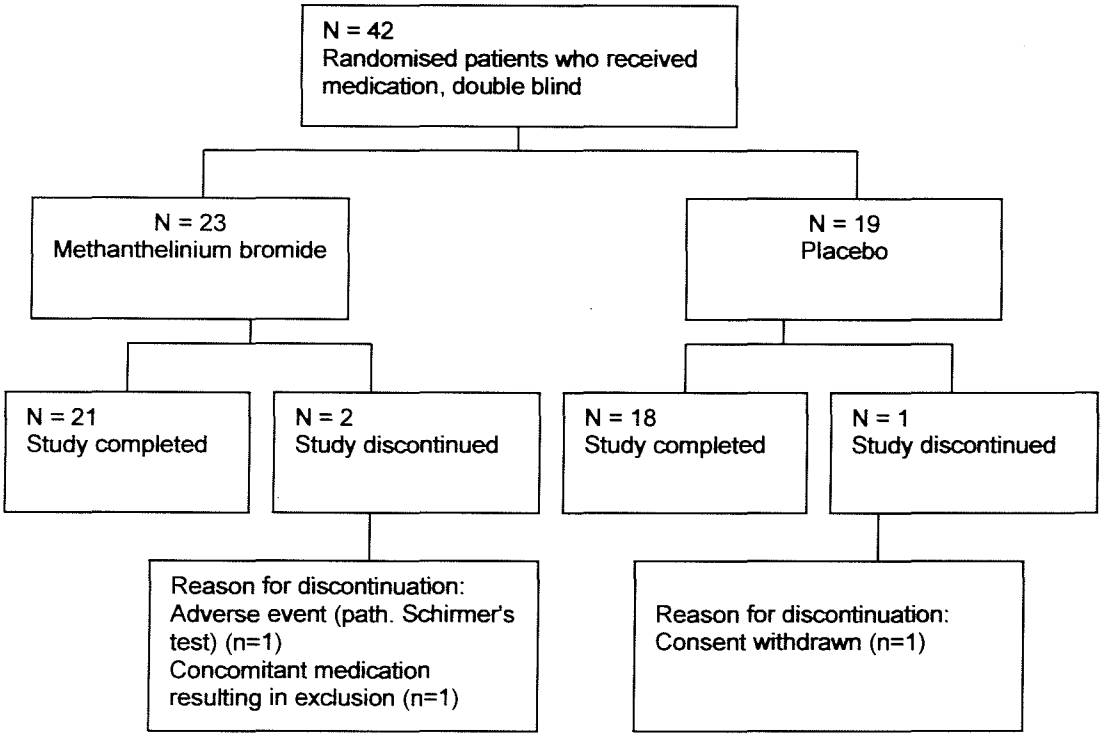

Figure 1: Overview of randomised patients. Distribution of patients to the methanthelinium bromide and placebo groups.

The mean individual percentage reduction in axillary sweat production during treatment was 25% ± 55% in the methanthelinium bromide group. In contrast, in the placebo group there was a mean individual percentage increase of 17% ± 66% (p = 0.02, Wilcoxon test).

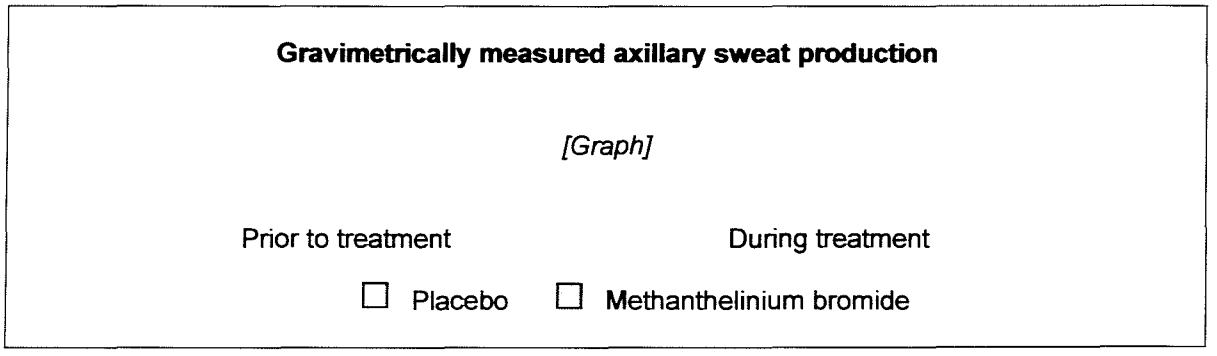

Figure 2: Gravimetrically measured axillary sweat production prior to and during treatment with 2 x 50 mg methanthelinium bromide.

For palmar hyperhidrosis the gravimeter values in the methanthelinium bromide group prior to treatment were 57.6 ± 38.4 mg/min, and in the placebo group 60.1 ± 31.9 mg/min (p = 0.68, Wilcoxon test). During treatment the values in the methanthelinium bromide group were 44.9 ± 28.8 mg/min, in the placebo group 50.2 ± 24.7 mg/min (p = 0.44, Wilcoxon test).
For sweat production in the hand area the individual percentage reduction during treatment was 14% ± 33% in the methanthelinium bromide group and 10% ± 25% in the placebo group (p = 0.44, Wilcoxon test).
Because the structure of the methanthelinium bromide and placebo groups was not the same in terms of patients with axillary hyperhidrosis, with considerably higher starting values in the gravimetric measurement in the methanthelinium bromide group, another explorative analysis which had not originally been planned was performed. In this analysis the gravimeter values prior

to treatment were compared to those during treatment separately for each of the two arms. The gravimetric measurement of sweat production in the axillary area reduced from 89.2 ± 73.4 mg/min before treatment to 53.3 ± 48.7 mg/min during treatment in the methanthelinium bromide group, corresponding to a difference of 35.9 ± 84.1 mg/min ($p = 0.02$, Wilcoxon test for connected samples). In the placebo group on the other hand the values remained almost unchanged at 60.7 ± 42.8 mg/min before treatment and 59.1 ± 40.6 mg/min during treatment, corresponding to a difference of 1.60 ± 39.94 mg/min ($p = 0.92$, Wilcoxon test for connected samples).

Subjective satisfaction with treatment
In week 4 around half of placebo and methanthelinium bromide patients were satisfied with the treatment: 9 out of 18 patients in the placebo group (50%) and 11 out of 21 patients in the methanthelinium bromide group (47.6%).

Side effects
Dryness of the mouth was the most common side effect in the methanthelinium bromide group. Dryness of the mouth occurred significantly more commonly in the methanthelinium bromide group than in the placebo group ($p = 0.01$ and $p = 0.02$, χ^2 test in weeks 2 and 4 respectively, table 1).
In terms of adverse effects which patients were specifically questioned about, such as pain on micturition, increase in heart rate, accommodation problems, increased intraocular pressure, skin changes, constipation there were no differences between the methanthelinium bromide group and the placebo group. The same is true of the other adverse events recorded. Schirmer's test 1 and 2 as a measure of the dryness of the eyes, blood pressure and pulse did not demonstrate any differences between the two groups either. No serious adverse events occurred.

Reduction in gravimetrically measured axillary sweat production during treatment

[Graph]

☐ Placebo ☐ Methanthelinium bromide

Figure 3: Reduction in gravimetrically measured axillary sweat production during treatment in the methanthelinium bromide and placebo groups.

Discussion

Oral anticholinergics are an established element of the treatment of generalised and treatment-resistant focal hyperhidrosis. The evidence available for this method of treatment for focal hyperhidrosis is limited to individual case reports and small case series, and this applies to both methanthelinium bromide and bornaprine [3, 4, 5, 6, 7, 8].
Until now no clinically controlled studies investigating the efficacy and safety of this preparation were available for the above indication.
The aim of this, the first clinically controlled double blind study, was therefore to investigate the efficacy and safety of oral methanthelinium bromide 2 x 50 mg/day in the treatment of focal hyperhidrosis.
In the ITT analysis, in which 41 patients were included, no difference between the methanthelinium bromide and placebo groups was seen in the absolute gravimeter values for axillary and palmar hyperhidrosis during treatment. The number of patients who experienced a reduction in the gravimeter values to <50 mg/min did not differ between the methanthelinium bromide and placebo groups either. However, there were differences in axillary hyperhidrosis between the methanthelinium bromide and placebo groups before treatment was commenced. The differences between the two groups became imperceptible during treatment. Because of the disparity in structure of the methanthelinium bromide and placebo groups efficacy could not strictly be established for the whole group. The disparity in the structure could be caused by the relative prevalence of younger patients with greater gravimeter values, i.e. more severe axillary hyperhidrosis in the methanthelinium bromide group. In order to avoid imbalances of this kind in

future trials of axillary hyperhidrosis, the age or the initial gravimeter values should be used for stratification.
Because of the disparity in structure, explorative analyses which were not planned in the original study protocol were carried out for the axillary location. A subgroup analysis of patients with gravimeter values of ≥ 50 mg prior to treatment showed a considerable difference between the two groups in favour of methanthelinium bromide. In addition, the methanthelinium bromide and placebo arms were examined separately in terms of differences in the gravimeter values during treatment compared with the initial values. In this assessment a significant reduction in gravimetrically measured sweat production was seen in the methanthelinium bromide group, while there was practically no change in sweat production in the placebo group.

Table 1: Frequency of dryness of the mouth (all patients)

Dryness of the mouth				
	Week 2 n = 41		**Week 4** n = 39**	
	Placebo	Methanthelinium bromide	Placebo	Methanthelinium bromide
Yes	2 (11.1%)	11 (47.8%)	1 (5.6%)	8 (34.8%)
No	16 (88.9%)	12 (52.2%)	17 (94.4%)	13 (65.2%)
p*	0.01		0.02	

* χ^2 test, two-sided
** Week 4: two values missing from the methanthelinium bromide group owing to patients discontinuing the study

When asked about their subjective satisfaction with the treatment, half the patients in each group stated that they were happy with the treatment. This could be because satisfaction could only be rated as a whole, so patients in the methanthelinium bromide group may have been satisfied with the effects of the preparation but perhaps rated their overall satisfaction lower because of the side effect of dryness of the mouth.
These data support the efficacy of oral treatment with 2 x 50 mg methanthelinium bromide in the treatment of refractory axillary hyperhidrosis. The data available did not demonstrate any evidence of clinically relevant efficacy of methanthelinium bromide in the treatment of palmar hyperhidrosis.
No serious adverse events occurred for the 41 patients. As expected, significantly more patients reported dryness of the mouth in the methanthelinium bromide group than in the placebo group.
Our results confirm the previous case reports and case series on the oral anticholinergics in the treatment of focal hyperhidrosis. *Fuchslocher* and *Rzany* [5] observed a 52 mg/min reduction in the gravimeter values for one patient with axillary hyperhidrosis during treatment with 2 x 50 mg methanthelinium bromide. There is also a case series (n = 12) on oral treatment with a different oral anticholinergic, bornaprine, presented by *Castells Rodellas* et al. [7]. In this case series, a "notable improvement in the symptoms" was seen in all patients in the space of 4 weeks. Because the dosage information for the bornaprine is contradictory in different sections of the paper and the method in which the iodine starch test was performed as an objective criterion remains unclear, this paper can only be interpreted to a certain degree, meaning that the two anticholinergics available in Germany cannot really be compared with one another.
Oral anticholinergics only represent *one* treatment option for axillary hyperhidrosis and should therefore always be viewed in relation to other treatment options.
Top of the list in the treatment of axillary hyperhidrosis is **aluminium chloride hexahydrate** [9, 10, 11, 12]. The methodology of the studies available differs. However, in summary it can be stated that the vast majority of patients treated were satisfied with the treatment. In terms of side effects, skin irritation was observed, in some cases in the form of miliaria-like skin changes [10] and itching [11].
The efficacy of **tap water iontophoresis** in axillary hyperhidrosis is disputed and depends on the type of device used. *Hölzle* and *Ruzicka* report in a case series with patients [13] poor efficacy of this treatment using a small battery-powered device. *Midtgaard* et al. [14] on the other hand talk

about predominantly excellent results which were achieved using a device similar to the conventional devices of today.

For one of the most recent treatment options for axillary hyperhidrosis, **intracutaneous botulinum toxin injections** there are two fairly large clinically controlled studies [15, 16], which have been able to clearly document the efficacy and tolerance of botulinum toxin injections in the treatment of axillary hyperhidrosis. The majority of side effects are described as mild or moderate; the only statistically significant difference between the botulinum toxin group and the placebo group was a subjective increase in sweat production at other sites on the body following treatment of the axillary hyperhidrosis with botulinum toxin (so-called compensatory sweating).

In addition to conservative treatment methods, there are also surgical methods of treating focal axillary hyperhidrosis. These are axillary suction curettage on the one hand and sympathectomy on the other. These surgical procedures are mostly only documented with case series.

Rompel and *Scholz* [17] documented 90 patients who underwent surgical removal of the axillary sweat glands by means of **curettage**. These ninety patients were compared with 23 patients who were treated with botulinum toxin. 91% of patients who underwent surgery and 96% of those treated with botulinum toxin reported that they would recommend the treatment. Side effects of the operation were partial epidermal necrosis, wound infections and haematoma. No side effects were observed for the treatment with botulinum toxin.

A reduction in sweat production of 38% by means of curettage was observed by *Proebstle* et al. [18]. Local side effects were scarring, induration, ecchymosis, pigmentation, partial alopecia, pain, paraesthesia, ulceration and seroma.

Endoscopic **thoracoscopic sympathectomy** (ETS) is comparatively a much more invasive procedure which can give rise to complications both during the procedure and in the short and long term after the operation [19, 20, 21, 22]. In the papers given, the most common side effect observed is compensatory hyperhidrosis (in some cases classed as intolerable). Less commonly, side effects such as pain/paraesthesia at the insertion site of the trocar [19, 20], respiratory pain [19, 20], largely transitory unilateral and bilateral symptoms of Horner's syndrome [19, 20, 22], ptosis and postoperative pneumothorax [19], gustatory sweating [19], bleeding, in some cases followed by open thoracotomy [20], and skin sensations when eating sweat, acidic or spicy foods [20] have been described.

Methanthelinium bromide has been used in the treatment of focal hyperhidrosis for many years. Until now, however, no clinically controlled studies were available on the efficacy and safety of this preparation, or of most of the other options for hyperhidrosis – with the exception of botulinum toxin A. In this study it was possible for the first time to establish a reduction in sweat production in the axillary area with good tolerance. Methanthelinium bromide was seen to have an effect in the methanthelinium bromide group of patients with axillary hyperhidrosis in comparison with the placebo group, although the two groups had very different initial values. It can nevertheless be assumed that methanthelinium bromide has an effect. In future studies it should be analysed using stratified sampling according to the initial gravimeter values.

Because dryness of the mouth occurs frequently, this treatment should be reserved for patients with systemic hyperhidrosis and those patients with focal hyperhidrosis who cannot be successfully treated with local treatment, e.g. aluminium chloride hexahydrate, alone. In such cases the targeted use of methanthelinium bromide as combination treatment with other forms of treatment can lead to a considerable improvement.

Conflict of interests

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