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Hydroxyzine premedication — does it provide better anxiolysis than a placebo?

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Objectives. To determine how effective hydroxyzine is compared with a placebo in providing pre-operative anxiolysis in our hospital population, and to assess the anxiolytic effect of our pre-operative visit.

Design. Double-blind, randomised, prospective, controlled trial. Anxiety levels assessed with visual analogue scales (VAS), by patient and investigator. Haemodynamic parameters measured: heart rate, blood pressure, respiratory rate.

Setting. Hillbrow Hospital, Johannesburg.

Participants. Sixty female patients aged 20 - 60 years, American Society of Anesthesiologists status I - III, scheduled for elective gynaecological surgery under general anaesthesia. The overall participation rate was 100%. All cases were randomly selected.

Intervention. Hydroxyzine (Aterax) 1 - 2 mg/kg, or a placebo administered orally as anaesthetic premedication.

Outcome measures. Anxiolytic effect of agents and of pre-operative visit. Time interval between premedication and induction of anaesthesia. Blood pressure, heart rate, respiratory rate, other signs of autonomic hyperactivity (restlessness, tremors, sweating).

Results. A statistically significant reduction in anxiety followed the administration of hydroxyzine ($P < 0.05$) and the placebo ($P < 0.03$); however, no statistically or clinically significant difference could be demonstrated between the two agents. No significant anxiolysis occurred following the premedication visit. The average premedication-induction interval was 72 minutes. There were no significant differences in haemodynamic parameters between the two groups.

Conclusions. Hydroxyzine, in the dose administered and after an appropriate premedication-induction interval, provided no better anxiolysis than a placebo in the pre-operative period. No significant anxiolytic effect was demonstrated by our routine premedication visit.

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Premedication is widely used before anaesthesia and surgery to reduce anxiety and immediate peri-operative awareness. Benzodiazepines are most commonly used for this purpose. Another frequently prescribed premedication drug is hydroxyzine (Aterax), an antihistamine with reported anxiolytic, sedative, analgesic, anticholinergic and anti-emetic effects.[1,2] Several studies[3,4] have suggested that pharmaceutical premedication may not be essential and that a properly conducted pre-operative visit with pre-anaesthetic counselling may be as beneficial in decreasing anxiety. The aims of this study were: (*i*) to determine the effectiveness of premedication with hydroxyzine in reducing pre-operative anxiety in our hospital patients scheduled for gynaecological procedures; and (*ii*) to compare it with a placebo. Other related aspects of the study were: (*iii*) to estimate the appropriateness of premedication timing with normal theatre routine; and (*iv*) to assess the potential anxiolytic effect of informing and reassuring the patient at the pre-operative visit.

Patients and methods

Approval from the University of the Witwatersrand Ethical Committee for Research on Human Subjects was obtained for the study. Sixty female patients (American Society of Anaesthesiologists (ASA) status I to III, aged 20 - 60 years) scheduled for elective gynaecological surgery under general anaesthesia signed informed consent to enter the trial. Patients who had been receiving any anxiolytic or sedative drugs, or who suffered from renal or hepatic insufficiency, were excluded from the study. The patients were randomly allocated to two groups (30 patients in each group) to receive either a placebo (thiamine) or hydroxyzine (plus thiamine) orally. In order to optimise the dose of hydroxyzine to the recommended 1 mg/kg, each group was further divided into two classes on the basis of estimated weight. Patients weighing less than 60 kg were given 50 mg hydroxyzine and those weighing 60 kg or more 100 mg. The study was conducted on a double-blind basis and the same investigator (J.B.) recorded all the observations on all the patients. A pre-operative visit was performed in the ward the night before surgery, when the anaesthetic and surgical procedures were explained to the patient and reassurance provided. The following morning the patient was seen again in the ward just before the premedication was administered by the ward sister. The patient was then transferred to the operating complex where she waited until theatre was ready. The patient was seen once more at the time of induction of anaesthesia. On the three different occasions — the night before surgery, the morning of surgery just before premedication, and at induction of anaesthesia — the following were assessed: (*i*) anxiety was rated separately by the patient and by the anaesthetist using a 100 mm visual analogue scale (VAS),[5,6] graded from 0 (totally relaxed) to 100 mm (extremely anxious); (*ii*) mean arterial pressure (MAP) and heart rate (HR) were measured by a non-invasive automated device (Dynamap); (*iii*) respiratory rate was counted over 1 minute; and (*iv*) any signs of sympathetic hyperactivity, such as restlessness, tremors and sweating, were noted. The time interval between administration of the premedication and induction of anaesthesia was recorded.

Statistical analysis of the results was performed with an analysis of variance (ANOVA) to compare anxiety levels pre-operatively in the two groups. An analysis of covariance was used to assess the effect of the premedication drug and type of surgery on VAS for anxiety; the weight and age of the patient and the baseline anxiety level were taken as covariates. Differences between groups were analysed with Student's *t*-test. The paired *t*-test was used for differences between repeated measurements on the same patients.

Results

There were no statistically significant differences between the two groups of patients in terms of age, weight, ASA status, and type of surgery (Table I). Relatively more patients in the hydroxyzine group weighed over 60 kg (80% compared with 63% in the placebo group). The average time interval between administration of the premedication and induction of anaesthesia was 72.2 minutes; this was similar for both groups (Table II). Five patients in each group, 17% in total, were induced less that 30 minutes after premedication, while 2 patients in the hydroxyzine group and 1 patient in the placebo group, 5% in total, received premedication more than 3 hours before induction of anaesthesia.

Table I. Patient characteristics

Characteristics	Placebo	Hydroxyzine	Total
Age (yrs)			
(mean ± SE)	44.8 ± 1.7	45.1 ± 2.0	44.9 ± 1.3
Weight			
< 60 kg	11	6	17 (28%)
> 60 kg	19	24	43 (72%)
ASA			
I	22	23	45 (75%)
II	8	6	14 (23%)
III	0	1	1 (2%)
Surgery			
TAH	13	11	24 (40%)
ICCS	9	9	18 (30%)
Laparotomy	2	6	8 (13%)
Cervical cone biopsy	3	1	4 (7%)
Laparoscopy	2	1	3 (5%)
TOP	1	0	1 (5%)
Urethral anastomosis	0	1	1 (2%)
DD & C	0	1	1 (2%)

TAH = total abdominal hysterectomy; ICCS = intracavitary caesium device insertion; TOP = termination of pregnancy; DD&C = diagnostic dilatation and curettage of the uterus.

Table II. Time interval between premedication and induction

Time (min)*	Placebo	Hydroxyzine	Total
Mean ± SE	72.7 ± 9.2	71.7 ± 8.9	72.2 ± 6.3
Range	15 - 195	15 - 180	15 - 195

* 30 observations in each group.

The patients showed unchanged anxiety levels on their VAS at the pre-operative visit (VAS 1) and the following day before administration of premedication (VAS 2). This was observed for both groups, and baseline anxiety for the two groups was similar (Table III). After premedication, there was a statistically significant decrease in anxiety, as was reported by the patients at induction of anaesthesia (VAS 3). This occurred in both the hydroxyzine group (> 20% decrease, $P < 0.05$) and the placebo group (> 50% decrease, $P < 0.03$) (Table III, a). The grading of patient anxiety by the investigating anaesthetist was consistently higher than the patient's own grading at all times (Table III, b). This probably relates to the fact that a total of 15 patients (7 patients in the hydroxyzine group and 8 in the placebo group) denied any anxiety (VAS = 0) throughout the pre-operative period. Exclusion of these patients when analysing the results helped to close the gap between the patient's and the anaesthetist's assessment. A decrease in anxiety was still demonstrated after premedication in both groups but was only statistically significant ($P < 0.005$) with the placebo (Table III, c). An analysis of covariance confirmed that level of anxiety was not influenced by the premedication drug, the type of surgery, or the age and weight of the patient. There were no statistically significant differences in the patients' MAP, HR or respiratory rate, either between groups or at the different times measured (Table IV).

Table III. Pre-operative anxiety levels*

VAS (mm)	Placebo	Hydroxyzine
(a) Patient's grading		
VAS 1	18.6 ± 4.1	11.2 ± 3.3
VAS 2	13.4 ± 3.8	11.9 ± 3.0
VAS 3	5.8 ± 2.1[b]	8.9 ± 3.0[a]
(b) Doctor's grading		
VAS 1	25.8 ± 2.8	24.4 ± 2.3
VAS 2	25.5 ± 2.6	26.7 ± 2.2
VAS 3	17.9 ± 2.1[a]	17.0 ± 2.9[a]
(c) Excluding patients denying anxiety†		
VAS 1	25.4 ± 4.9	14.6 ± 4.1
VAS 2	18.2 ± 4.7	15.5 ± 3.7
VAS 3	7.9 ± 2.7[c]	11.6 ± 3.7

* Anxiety level was measured by means of a visual analogue scale (VAS) graded from 0 (no anxiety) to 100 mm (extremely anxious). Values represent means (± SE) of 30 observations unless stated otherwise. VAS 1 refers to the level of anxiety measured at the premedication visit, the night before surgery. VAS 2 was measured just before the administration of the premedication. VAS 3 was measured just before the induction of anaesthesia.
† Derived from (a). Placebo group = 22 patients, hydroxyzine group = 23 patients.
Significant differences between VAS 1/2 and VAS 3 measured with the paired *t*-test:
[a] $P < 0.05$.
[b] $P < 0.03$.
[c] $P < 0.005$.

Table IV. Physiological measurements* before and after premedication

	Placebo			Hydroxyzine		
	T1	T2	T3	T1	T2	T3
BP (mmHg)	103 ± 2	102 ± 2	102 ± 3	106 ± 3	102 ± 2	104 ± 3
HR (/min)	82 ± 3	82 ± 3	83 ± 3	79 ± 2	81 ± 3	81 ± 3
RR (/min)	18.7 ± 0.8	18.3 ± 0.6	19.0 ± 0.6	19.0 ± 0.7	18.1 ± 0.6	18.1 ± 0.7

* Means (± SE) of 30 observations in each group.
BP = mean systemic blood pressure; T1 = the night before surgery; T2 = the morning of surgery; T3 = at induction of anaesthesia.

Signs of autonomic hyperactivity (restlessness, tremors or sweating) were observed in a total of 13 patients (22%), 5 in the placebo group and 8 in the hydroxyzine group. These signs were most evident before premedication with the placebo (6 out of 7 times) and as frequently before as after premedication with hydroxyzine (4 versus 5 times, respectively).

Discussion

This study was designed to assess how effective premedication with hydroxyzine was in relieving pre-operative anxiety in our hospital population scheduled for elective gynaecological surgery.

Hydroxyzine, a piperazine derivative, is a unique non-phenothiazine tranquilliser. Sedation is probably effected by blocking central histamine H_1 receptors, and anxiolysis by subcortical depression.[7] Other advantageous actions include skeletal muscle relaxation, bronchodilatation, and anti-histaminic and anti-emetic effects.

The recommended dose in adults is 50 - 100 mg (1 - 2 mg/kg), as was used in this study. The onset of action is 15 - 30 minutes after oral administration. The duration of action is between 4 and 6 hours, with an elimination half-life of 2.97 hours. Mean peak plasma levels are attained 3 hours after administration.[8-11] In this study the average interval between premedication and induction of anaesthesia was 72 minutes, which is well within the recommended range. Only 22% of the patients were induced either less than 30 minutes or more than 3 hours after premedication, thereby not receiving the possible full benefit of the drug. The majority of the patients were thus under the influence of the premedication drug at the time of anaesthesia and surgery. This seems to be satisfactory, considering the system used at our institution where patients are sent for theatre as the surgical list progresses and are premedicated when the trolley arrives to convey them to theatre.

In this study, we failed to demonstrate a specific anxiolytic effect of hydroxyzine in the pre-operative period, despite using recommended dosages and allowing for appropriate time of action. A consistent anxiolytic effect of similar extent was observed after administration of either thiamine or hydroxyzine plus thiamine. We do not know of any evidence to suggest that thiamine has any specific anxiety-reducing action or that thiamine may impair the desired effects of hydroxyzine. We therefore ascribe our results to a placebo effect. It was of interest that this placebo-anxiolysis was reported by both the patient and the investigator, as shown on their separate and independent VASs.

Other studies have also failed to show a convincing anxiolytic effect of hydroxyzine. Premedication with intramuscular hydroxyzine appeared only slightly superior to placebo in alleviating apprehension in patients undergoing minor gynaecological procedures. Fifty-four per cent of patients were calmed with hydroxyzine, compared with 34% with the placebo.[2] A comparison of alprazolam with hydroxyzine as oral premedication showed no anxiolysis with the latter drug in patients scheduled for a variety of surgical procedures;[12] in fact, a slight increase in anxiety was observed following the hydroxyzine premedication. Similarly, poor anxiolytic effects of intramuscular hydroxyzine when compared with midazolam for premedication have been reported in patients undergoing hysterectomy.[13] Another comparison of intramuscular hydroxyzine with lorazepam[14] pointed out the lack of adequate anxiolysis and amnesia with the former agent for surgical premedication. In this study lorazepam, but not hydroxyzine, was considered significantly superior to placebo by the patients.[14] Intravenous premedication with hydroxyzine (75 mg or 150 mg) provided only mild anxiolysis and scored consistently lower than 15 mg intravenous diazepam.[14] Clinical trials on premedication where placebos are used show that about 30% of patients report decreased apprehension after receiving the placebo.[2,14,15] This is comparable to the findings in the present study. After administration of the placebo, and excluding the patients who denied any baseline anxiety, 32% of the patients (7 out of 22) expressed a decreased anxiety level. A similar proportion, 35% (8 out of 23), was found in the group receiving hydroxyzine.

Recommended doses of hydroxyzine (75 mg orally or 50 mg intramuscularly), corresponding to about 1 mg/kg, were also administered in these studies. It has been suggested of late by the manufacturer of Aterax (UCB) that this dose may not be adequate and that 3 - 5 mg/kg may provide better anxiolysis without detrimental side-effects.

The present study did not show a reduction in anxiety following the pre-operative visit, as has been reported on several occasions.[16-19] The anxiety level remained the same the night before surgery and just before premedication, anxiolysis being apparent only after the drug was administered. Our routine pre-anaesthetic visit consists of assessing the medical condition of the patients and then informing and reassuring them about the planned surgery. A previous study (D. Hopkins and C. Mailovitch — unpublished data) conducted at our hospital suggested that most of our patients do not know what to expect with regard to anaesthesia and surgery. Adequate pre-operative counselling by surgeons, ward staff and even anaesthetists is often lacking and raises doubt about the validity of informed consent in this context. Furthermore, a significant number of patients deny any pre-operative anxiety. This was also a finding for 38% of the patients in the present study. The importance of the patient's social class in the way the placebo effect is generated has been emphasised.[20] In lower socio-economic classes, to which the majority of our patients belong, a placebo in the form of a drug is more effective. In higher socio-economic groups a psychotherapeutic placebo, such as pre-anaesthetic counselling, is more appropriate. It is also of interest that providing detailed information to the patient about the risks of anaesthesia and surgery does not seem to increase[21] or decrease[17] pre-operative anxiety.

In conclusion it appears that, in our hospital patients, hydroxyzine offers no significant advantage over a placebo in providing anxiolysis in the pre-operative period. A routine pre-anaesthetic visit which includes informing, explaining and reassuring seems to have little effect in reducing anxiety, which in any case is often denied by patients. The importance of the placebo effect of administering 'a tablet' should not be overlooked and may be more effective than pre-anaesthetic counselling alone.

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