

PHYSIOLOGICAL EFFECTS OF TRIMPERAZINE AS PREMEDICATION FOR DENTAL TREATMENT IN PRESCHOOL CHILDREN

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قيمت هذه الدراسة تأثير الجرعات المختلفة من ثلاثي البرازين (فالرجان) على العمليات الفسيولوجية الحيوية والتأثيرات الجانبية للعقار على ٣٠ طفلاً وطفلة مادون سن الخامسة واشترط في الاختيار أن يكونوا أصحاء وغير متقبلين للعلاج .

قيس كل من ضغط الدم والنبض وتركيز الأوكسجين أثناء المراحل المختلفة للعلاج باستعمال جهاز الدينامام واستخدم جدول تحليل التباين لدراسة تأثير الجرعات المختلفة على المؤشرات الحيوية .

لوحظ أنه بالرغم من وجود علاقة عكسية بين الجرعات المختلفة للعقار وضغط الدم والنبض فإن الجرعة القصوى للعقار لم تستطع أن تعكس تأثير الارتفاع البسيط في المؤثرات الحيوية المصاحبة لعملية حقن المخدر الموضعي أو وضع العازل المطاطي والبدء في حفر الأسنان .

من العيوب الملاحظة عند استعمال هذا العقار طول المدة اللازمة لفعاليتها (من ساعة إلى ساعتين) ولانتهاء الفعالية (٣ - ٨ ساعات) .

لوحظ أيضاً ازدياد العطش المصاحب للجرعات العالية (٤ مجم/كجم) ولذا لا ننصح باستعماله للأطفال الذين يعانون من الجفاف .

This study evaluated the effect of different doses of trimeprazine on some physiological parameters and the side effects of the drug in 30 healthy but uncooperative preschool children who were undergoing dental treatment. Changes in systolic and diastolic blood pressure, pulse rate and oxygen saturation (SaO₂) were assessed during specific treatment procedures in relation to the different doses of the medication. Descriptive statistics and ANOVA model with interaction were used to analyze the effects of drug dosage and dental procedures on the physiological parameters. In spite of the inverse relationship between blood pressure and pulse rate with the dose of trimeprazine used, the highest dose of the drug could not counteract the effect of dental treatment so that the systolic and diastolic blood pressure as well as pulse rate were significantly affected by dental treatment in these children. However, trimeprazine proved to be an effective sedative and antiemetic with little or no anxiolytic effect. Other side effects observed were prolonged onset of action, delayed recovery from drug effect and increase in thirst hence the drug may not be suitable for a dehydrated child.

Introduction

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Premedication is used primarily to allay anxiety and provide a more relaxed feeling during dental treatment, particularly in pediatric patients. It facilitates provision of quality dental care for an uncooperative child.

Trimeprazine tartrate (Vallergan[®]) is a phenothiazine which is widely used both as a premedicant and as a general pediatric sedative.¹⁴ Many studies have shown the effectiveness of this

Table 1. Groups of patients by age, weight and dose.

Groups	Age (mo) Mean \pm SD	Weight (kg) Mean \pm SD	Dose of Vallergran
1	43 \pm 6	15.1 \pm 1.8	0.0 mg/kg (control)
2	41 \pm 9	14.7 \pm 2.2	2.5
3	42 \pm 9	14.7 \pm 1.8	3.0
4	45 \pm 10	14.5 \pm 2.4	3.5
5	43 \pm 13	14.4 \pm 4.4	4.0

N = 8 for each group

medication when used alone⁵ or in combination with other drugs,^{4,6,7} prior to induction of general anesthesia. Its use as dental premedicant has been suggested,⁸ but there appears to be no clinical studies to that effect. Recently, we investigated the efficacy of different dosages of trimeprazine as premedication for uncooperative pediatric dental patients.⁹ In this report, the effects of trimeprazine on physiological parameters such as changes in blood pressure, pulse rate, arterial oxygen saturation [SaO₂], duration of drug action and other untoward effects are presented.

Materials and Methods

The study group comprised thirty uncooperative children on whom 40 sedation procedures were carried out. The children had negative medical histories for abnormal, emotional or mental development and none had medical conditions such as hepatic or renal disorders which would contraindicate the use of trimeprazine. The subjects were selected from the general population of patients who attended the pediatric dentistry clinic of the King Saud University, College of Dentistry in Riyadh. Informed consent was obtained for all sedation procedures after which preoperative instructions were given to each patient.

When the children presented for treatment, they had eaten nothing by mouth (NPO) from midnight before the morning of each appointment so as to enhance absorption of the medication and prevent the hazard of vomiting and aspirating food recently consumed. Assessment and monitoring of each child was carried out by the attending anesthesiologist. The patients were weighed and baseline values obtained for blood pressure, pulse rate and SaO₂ for each child. The children were randomly assigned to one of five groups. The first

group which served as control was given mixed fruit juice. The second, third, fourth and fifth groups had 2.5, 3.0, 3.5 and 4.0 mg/kg, respectively, of Vallergran syrup forte administered by a nurse in a double blind fashion (Table 1), the details of which had been described earlier.⁹ Two hours following drug administration, the child was taken into the operatory and restrained after the monitors were placed. Local anesthetic was given and restorative treatment was carried out. Rubber dam isolation was used in all cases to protect the airway and prevent aspiration of any foreign object except during extractions. The operative procedures lasted between 30 minutes and 75 minutes with an average time of 50 minutes per patient. Readings for blood pressure, pulse, SaO₂ were taken at 5-minute intervals and also during local anesthetic injection, rubber dam fixation, cavity preparation and amalgam filling and carving. All patients were monitored using Dinamap[®] 1846 SX vital signs monitor with oxytrak pulse oximeter. Upon completion of dental treatment, the child was taken to the recovery room for observation and further monitoring. The child was discharged to the parents care when vital signs were stable and the child was sufficiently awake and could hold his/her head up, walk or move with coordination. Appropriate post-operative instructions were then given. Telephone contact was made with the parents the following day to find out whether the patients experienced nausea/vomiting, thirst, fever, sleeping disorder, swelling or other untoward effects. They were also asked about the state of the child on getting home, whether awake, drowsy, or sleepy and the eventual time that the child was fully awake with no sign of drowsiness. From this we estimated the duration of drug action.

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Table 2. Mean \pm SD values for systolic pressure as a function of dose across dental procedures.

Dose groups	Dental Procedures						
	Baseline	Preop	LA	RD	CAV	FIL	Postop
1	105 \pm 7	115 \pm 9	126 \pm 6	125 \pm 7	122 \pm 7	106 \pm 13	108 \pm 12
2	99 \pm 9	99 \pm 13	118 \pm 9	115 \pm 6	117 \pm 9	102 \pm 8	105 \pm 9
3	103 \pm 14	94 \pm 8	111 \pm 9	111 \pm 11	115 \pm 12	97 \pm 15	104 \pm 10
4	106 \pm 10	101 \pm 14	114 \pm 11	112 \pm 7	108 \pm 12	103 \pm 11	98 \pm 5
5	98 \pm 9	93 \pm 11	109 \pm 10	109 \pm 12	105 \pm 7	99 \pm 9	102 \pm 6

Table 3. Mean \pm SD values for diastolic pressure as a function of dose across dental procedures.

Dose groups	Dental Procedures						
	Baseline	Preop	LA	RD	CAV	FIL	Postop
1	66 \pm 4	67 \pm 3	69 \pm 5	68 \pm 4	66 \pm 4	62 \pm 4	61 \pm 5
2	63 \pm 10	60 \pm 7	63 \pm 4	65 \pm 4	64 \pm 4	59 \pm 4	60 \pm 7
3	61 \pm 6	56 \pm 8	63 \pm 7	58 \pm 8	61 \pm 7	54 \pm 7	56 \pm 6
4	62 \pm 3	61 \pm 3	64 \pm 7	62 \pm 3	63 \pm 4	59 \pm 5	58 \pm 3
5	56 \pm 4	55 \pm 5	58 \pm 6	57 \pm 6	57 \pm 6	53 \pm 4	57 \pm 2

For valid comparison between different groups, the need for uniform procedure for each patient was considered. Descriptive statistics were used to summarize the physiological variables in each treatment group and for each dose. In order to assess the effects of drug dosage and procedures or treatments on the physiological variables, a two-way analysis of variance model with interaction was fitted to the data. The baseline values of the variables were first compared. The interaction effect was examined and if not significant, interest was concentrated on the main effects of treatment and dosage. For significant main effects, pairwise comparison was undertaken using the residual error mean square and the student t-test to check for statistical significance which was fixed at the 5% level. The Mantel-Haensel Chi-square statistic was used to test significance of the linear trend in proportion with side effects with increase in dosage of the drug. The odds ratio, using the control group as reference category, was used to estimate the risk of dosage.

Results

The study included 17 boys and 13 girls between the ages of 30 and 60 months with a mean age of 42.8 months. The children ranged in weight from 10 to 20 kg with a mean weight of 14.7 kg.

Table 4. Analysis of variance, F ratio and probability for dose procedure and interaction of physiologic parameters studied.

Parameter	Dose	Procedure	Interaction
Systolic	10*	17	0.7
	(0.001)**	(0.001)	(0.75)
Diastolic	16.7	9.9	0.4
	(0.001)	(0.001)	(0.95)
Pulse rate	33.5	21.3	0.68
	(0.001)	(0.001)	(0.77)
S _a O ₂	24.3	11.7	0.79
	(0.651)	(0.293)	(0.862)

* F ** Probability

Systolic and Diastolic Blood Pressure

Tables 2 and 3 show the mean values for systolic and diastolic blood pressure, respectively, as a function of dose across different dental procedures. Comparison of the mean values of baseline systolic and diastolic pressure between five-dose-groups using one-way ANOVA showed no statistical significance ($P > 0.05$). A two-way ANOVA was then used to examine the main effects of dose and procedure as well as their interaction on systolic and diastolic blood pressure. A non-statistically significant interaction effect was observed ($P > 0.05$ for both systolic and diastolic) implying that the main effects only are of importance (Table 4). Patients in group 1 (0.0 mg/

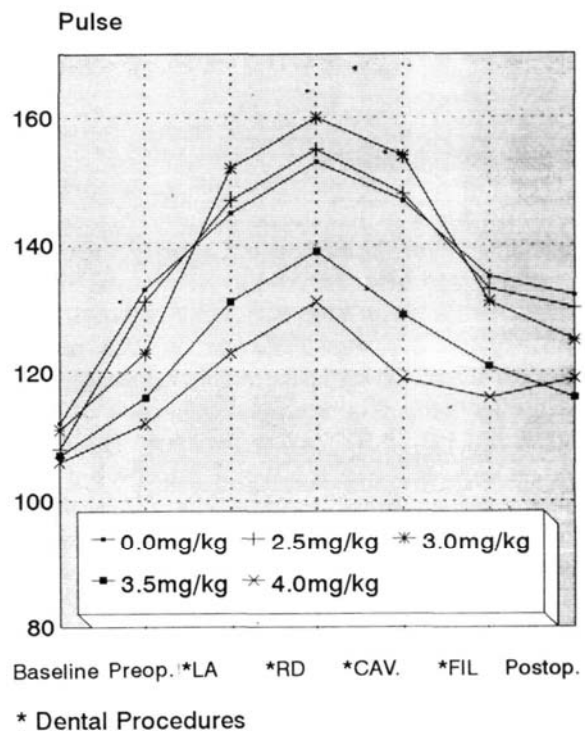
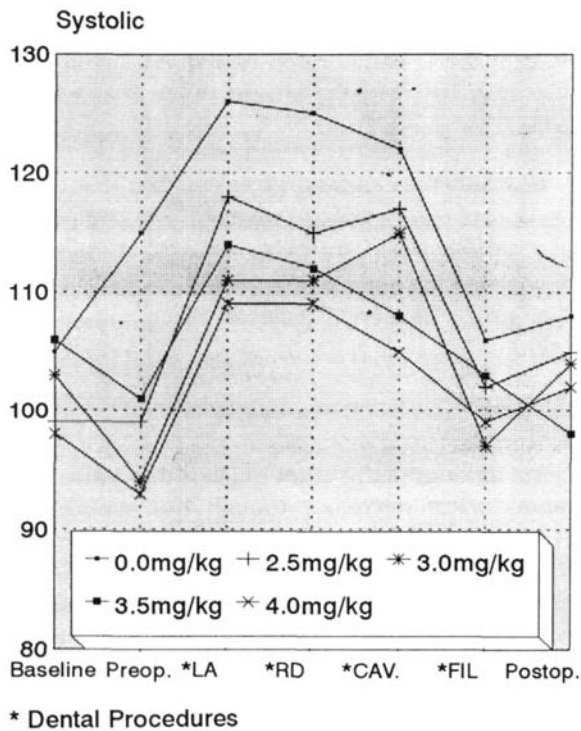


Figure 1. Systolic blood pressure during treatment for different doses of Vallergran.

Figure 2. Pulse rate during treatment for different doses of Vallergran.

Table 5. Mean ± SD values for S₀, as a function of dose across dental procedures.

Dose groups	Dental Procedures						
	Baseline	Preop	LA	RD	CAV	FIL	Postop
1	98 ± 1.9	97 ± 3.2	98 ± 3.1	96 ± 3.9	96 ± 3.9	96 ± 1.8	97 ± 2.1
2	98 ± 2.1	97 ± 2.5	97 ± 2.0	97 ± 3.1	96 ± 2.7	96 ± 2.5	97 ± 1.6
3	96 ± 3.1	97 ± 2.7	96 ± 1.9	96 ± 4.2	95 ± 1.9	95 ± 3.9	98 ± 1.2
4	97 ± 2.9	99 ± 2.1	98 ± 1.8	98 ± 3.7	97 ± 2.7	97 ± 3.1	97 ± 2.3
5	97 ± 1.7	98 ± 1.9	97 ± 2.5	97 ± 2.9	96 ± 1.5	98 ± 1.9	96 ± 2.8

kg) exhibited significantly higher blood pressure than the other four (2, 3, 4, and 5) dose-group ($P > 0.05$) in each pairwise comparison following local anesthetic administration. The increase in blood pressure diminished with higher dose of the drug. There was a tendency for this effect to decline slowly towards the end of treatment especially during amalgam filling and carving [Fig. 1].

Pulse Rate

Dose-effect and treatment procedures had statistically significant influence on pulse rate ($P <$

0.05). There was an inverse relationship between the dose of Vallergran and pulse rate. However, the pulse rate increased significantly from baseline during local anesthetic administration and rubber dam application and remained elevated during cavity preparation before it decreased towards the end of treatment [Fig. 2].

Arterial Oxygen Saturation [Sa₀]

There was no specific trend of changes in Sa₀, before, during and after treatment (Table 5). The mean percentage oxygen saturation for all subjects

varied between 95% and 99%. Analysis of variance showed no statistical significance at 0.05 level.

Duration of Drug Effect

None of the subjects in Group 1 experienced any sedation during or after the procedure. For subjects receiving 2.5 mg/kg Vallergran (Group 2), the effect of drug lasted between 2 hours 45 minutes and 4 hours with a mean time of 3.3 ± 0.4 hours. For those given 3.0 mg/kg (Group 3); 3.5 mg/kg (Group 4) and 4.0 mg/kg (Group 5); the duration of drug effect ranged between 4.5 - 8 hours; 5 - 8.5 hours and 4.6 - 8.6 hours, respectively. The mean values were 6.2 ± 1.3 ; 6.8 ± 1.1 and 6.6 ± 1.3 hours, respectively. One-way ANOVA showed that the mean values for 3.0, 3.5 and 4.0 mg/kg were significantly different from that of 2.5 mg/kg ($P < 0.05$). Further analysis showed no significant difference in duration of drug effect between doses of 3.0; 3.5 and 4.0 mg/kg, respectively ($P > 0.05$).

Prevalence of Untoward Effects (Table 6)

Nausea/vomiting: None of the patients experience nausea or vomiting in all groups.

Thirst: A direct relationship was observed between the dose of the drug and the number of people who complained of thirst. Group 3 subjects had four times chance of being thirsty compared with Group 2. The chance increased to twenty-one and forty-nine times for Groups 4 and 5, respectively, according to odds ratio relative to the control group.

Fever: A rise in body temperature was reported by some patients in all groups. Two patients, one each in Groups 2 and 4, required the use of

antipyretic (Tempra). However, Chi-square analysis for linear trend revealed no significant difference between the groups ($X^2 = 0.413$ $P > 0.05$).

Swelling: Two patients (25%) in Group 4 were reported to have had some swelling on the face and one patient each (13%) in Groups 3 and 5. However, chi-square test revealed no statistically significance difference between the groups ($P > 0.05$).

Discussion

The findings of this study suggest that Vallergran causes some decrease, though not statistically significant, in blood pressure in children. Similar observation was reported in previous studies.⁴¹⁰ However, following the start of dental procedures, the blood pressure rose significantly higher than baseline values and peaked with the administration of local anesthetic or rubber dam application before returning toward baseline values at the end of the treatment. The pulse rate demonstrated a similar trend. This is not unexpected since the pulse is related to cardiac output which influences the systolic pressure.¹¹ Pulse rate is reported to increase in the dental environment because of fear and anxiety.¹²¹⁵ Monitoring pulse rate during dental treatment may be helpful in determining the effectiveness of anxiety-reducing drugs commonly used in dental treatment of uncooperative children.¹²¹³ It is surprising to note that the increase in blood pressure and pulse rate, both physiological expressions to physical stimulation caused by the injection, could not be suppressed by the higher dose of Vallergran used in this study. Although the changes in blood pressure and pulse rate were statistically significant, they were much

Table 6. Prevalence of untoward effects.

Nausea/Vomiting	Group 1	Group 2	Group 3	Group4	Group 5
	0	0	0	0	0
Thirst*	0	1 (13%)	3 (38%)	6(75%)	7(88%)
Fever	1 (13%)*	2(25%)	3 (38%)	4 (50%)	3 (38%)
Swelling	0	0	1 (13%)	2(25%)	1 (13%)

* No. of subjects affected. Bracketed number = percentage of total. May not equal 100% due to rounding

+ $X^2 = 10.722$, $P < 0.001$

All other comparisons $P > 0.05$

smaller with the high dose of Vallergran. This implies that despite the sedative effect mediated by the high dose compared to other doses, there was no corresponding anxiolytic effect; if anything, the treatment caused more of excitement. Clinically, significantly high doses of Vallergran may be needed to counteract the influence of some dental procedures in uncooperative children. But high doses will, in many cases put the child in an unconscious state.¹¹ It is therefore, essential that clinicians using sedative drugs be aware of this fact and weigh all other options. Continuous monitoring of patient responsiveness and vital signs are imperative. Vital signs are most helpful in monitoring medication effects on the cardiovascular system and particularly giving early warning of over-sedation.¹⁴ No compromised situation was observed with the doses used in this study, however, we noticed that some of the children were more sedated following the 4.0 mg/kg dose.

Since the SaO₂ on the average remained above 95% in all groups, it may be inferred that no significant respiratory depression was produced during sedation by any of the doses studied. Wilson¹⁵ observed that most desaturations recorded during pediatric dental sedations were due to inadvertent airway partial obstructions as a result of flexion of the neck of patient caused by manipulations in the oral cavity. We took care of this by placing a roll of towel behind the neck of the patient in order to extend it. Despite this, occasional hypoxemia (brief desaturations) were observed especially in the low dose group. This is thought to have been due to sustained apneic responses as a result of local anesthetic injection, crying or sobbing.

The sedative efficacy of Vallergran is not in doubt when optimum dose is administered. Orally administered. Vallergran takes 1-1/2-2 hours to attain peak effect.¹⁶ This long waiting period before treatment could commence has the possibility of increasing the level of anxiety among the patients. The duration of its central nervous system effects is variable and dose related. A small dose of 2.5 mg/kg which is not effective for dental treatment provides sedation lasting over 3 hours while an optimum dose of 3.5 or 4.0 mg/kg provides an effect lasting over 8 hours. Similar findings have been noted previously.^{2, 7} This sedation/recovery

time is quite prolonged and may be a disadvantage for day care dental sedation, even though patients are readily rousable and protective reflexes have not been compromised. A drug that has rapid onset and optimum duration of action of about one hour would be most appropriate for pediatric dental sedation on outpatient basis.

None of the subjects in the study group experienced nausea/vomiting pre or post-operatively. This finding confirmed previous studies.^{6,7,18} The antiemetic property is very desirable of any medication to be used for sedating children. Vomiting and the consequent possibility of aspiration could be prevented.

In comparison with the control group, there was a significant linear trend in proportion of thirst postoperatively with increase in dosage of Vallergran. Virtually, all patients that had 4 mg/kg requested water to quench their thirst after recovering from effect of the drug compared to 13% of those who were administered 2.5 mg/kg. This observation was not reported in other studies where Vallergran was used.^{2,13,57,17} This was probably due to the intravenous infusion given to those patients to obviate any dehydration. Our patients had nothing by mouth for over 8 hours as a premedication requirement and parenteral administration of fluids is not possible during conscious sedation because of disruptive behavior of the patient. This side effect of Vallergran gives it an obvious disadvantage and it may therefore, not be suitable for use as a dental premedicant in a dehydrated child.

The rise in body temperature experienced by some patients cut across all groups. Even though that was a subjective finding reported by the mothers over telephone, no correlation was found between the rise in temperature and dose of medication given. Transient phase of bacteremia is not uncommon during dental manipulation.¹⁸ Because of disruptive attitude, some of the patients did not have regular dental care hence they presented with poor oral hygiene and gross caries necessitating some extractions or pulp treatment apart from restorative treatment. Such factors as bacteremia, tissue damage and dehydration are known to have been responsible for postoperative temperature elevation.¹⁹

Of the four patients who reported some swelling on the face, one had inflammatory edema

following multiple exodontia that resolved two days later after antibiotics therapy. No obvious swelling was seen in the other three patients when they were recalled immediately following the complaint.

Conclusions

When used alone, Vallergran caused a fall in systolic and diastolic blood pressures. However, this fall in cardiovascular parameters was reversed with a statistically significant increase during delivery of dental treatment. The increase was less with high dose of Vallergran than low dose or placebo. There was no significant respiratory depression caused by any of the doses studied.

When given orally, Vallergran has a prolonged onset of action and delayed recovery time which may create a long-lasting unnecessary tension and which may find it inconvenient. It causes thirst, hence it may not be suitable to give to a dehydrated child. It does not cause nausea/vomiting, fever or swelling when used for dental premedication. Nevertheless, this medication may not fall into the category of ideal drugs for use in conscious sedation for dental procedures in children.

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