A STATISTICAL ANALYSIS OF THE EFFECTS OF Bzd IN THE PREVENTION AND MANAGEMENT OF ORAL MUCOSITIS

by

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Title of Thesis/Project/Extended Essay

A STATISTICAL ANALYSIS OF THE EFFECT OF BENZYDAMINE (BZD) IN THE PREVENTION AND MANAGEMENT OF ORAL MUCOSITIS

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ABSTRACT

This project reports on the anlysis of a data set from an oral radiation therapy study conducted by the Cancer Control Agency of British Columbia. The researcher who collected the data (Dr. Joel Epstein) had four major objectives:

1) to determine the efficacy of a drug Benzydamine,(Bzd) for the reduction of perceived pain;
2) to determine the efficacy of the drug (Bzd) for the reduction of tissue breakdown;
3) to determine the effect of radiation to the salivary glands on the amount of saliva;
4) to determine whether the increased amount of saliva was associated with a reduction in tissue breakdown.

A variety of regression models are identified and their parameters estimated: cumulative logit, analysis of variance, and multiple regression. Residual analysis is used to check the adequacy of the fitted regression models. Both descriptive and inferential strategies are used to assess the data. The main scientific conclusions are: Bzd is not sufficient to reduce pain, but it does reduce the breakdown of healthy tissue; the type of radiation used is effective in increasing the amount of saliva produced, and finally, the increased saliva is associated with a slight reduction in tissue breakdown.

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DEDICATION

To my family -

especially my mother and eldest brother Abdie, without whose faithful love and support none of this would have been possible.

TABLE OF CONTENTS

LIST OF TABLES

Table **Page**

LIST OF FIGURES

Figure Page

I. INTRODUCTION

This project focuses on the data collected in a 1987 study by Dr. Joel Epstein, a dentist with the Cancer Control Agency of British Columbia. Dr. Epstein's study examined the effectiveness of the drug Benzydamine (Bzd) as a pain-killer and in the prevention of the breakdown of healthy tissue. The effect of radiation on the amount of saliva and the subsequent tissue breakdown was also examined.

An earlier, informal trial of a Bzd mouth rinse in the management of chemotherapy-induced mucositis, or inflammation of the mucous membranes, had reported palliation in seven of nine patients (Sonis and colleagues); and these results suggested the advisability of a controlled clinical study.

Dr. Epstein's objective was to study the use of Bzd in a double-blind, placebo-controlled trial, where patients received radiation therapy to the oropharyngeal region for the treatment of cancer. The study was to assess the potential anti-inflammatory effects of the Bzd rinse and its application in the prevention and management of oral mucositis.

The study's four major scientific objectives were:

1) to determine the efficacy of a drug Benzydamine, (Bzd) for the reduction of perceived pain;

2) to determine the efficacy of the drug (Bzd) for the reduction of tissue breakdown ;

3) to determine the effects of radiation to the salivary glands on the amount of saliva;

4) to determine whether an increased amount of saliva was associated with a reduction in the tissue breakdown.

II. STATISTICAL DESIGN & METHODS OF ANALYSIS

i) The Experiment

Forty-three patients scheduled to receive radiation therapy to the oropharyngeal region were eligible for the study. Patients were excluded from the study if they did not provide informed consent, were younger than 18 years of age, had liver disease, or were hypersensitive to Bzd. Consenting patients were allocated at random to receive either the drug (Bzd) or the placebo rinse. The rinses were dispensed in a double-blind manner. The total sample size was 43 patients, broken down into two groups: the Bzd group, consisting of 25 patients; compared to the placebo group, consisting of 18 patients. The difference in the size of the two groups was due to the sequential nature of the randomization procedure, and the fact that six patients from the placebo group dropped out of the study. The reasons for this lack of compliance will be discussed in the concluding section of this paper.

In order to study the subjective evaluation of pain and other symptoms during treatment, patients were requested to complete visual analog scales (VAS). The VAS provided the rank score of a patient's self-evaluation of symptoms. To determine the efficacy

of Bzd for the reduction of percieved pain, the original data was measured through the VAS, ie., patients recorded their pain on a scale of 0 to 10, where 0 means no pain and 10 maximum pain.

The severity of tissue breakdown was graded by the size of the area of involvement, severity of inflammation, total inflammation of surface involved, maximum size of ulceration, and total area of ulceration for each surface of the oral cavity involved. For clinical reasons, the inflammation score was multiplied with the other variables: the area of reaction * severity of inflammation; the severity of inflammation per surface involved; and the area of reaction * severity of inflammation per surface involved; in order to provide a combined score for mucositis that was more representative of the severity of tissue reaction.

The three types of radiation were: high dose bilateral, high dose unilateral, and low dose. Each of these were pre-selected by the investigator, whose question of interest was whether or not the type of radiation affects the amount of saliva measured at rest and during stimulation. The two measures of saliva levels were collected at the same time of day on each visit - either mid-morning or mid-afternoon. The measurements of the pain were taken at weekly intervals, as were the tissue breakdown and the saliva levels.

ii) The Data Structure

For each of the forty-three patients, data for the following variables were available:

The response variables were:

a) the eight visual analog scales measurements of Pain. These were originally categorized 0 to 10, but inorder to achieve convergency of estimatores the ten categories were reduced to four categories, (ie. none, minimal, normal, and severe):

1) burning at rest

2) burning with eating

3) pain at rest

4) pain with eating

5) burning with drug

6) taste of drug

7) analgesia drug

8) over-all drug (total pain)

b) the eight measures of tissue breakdown (TBD):

1) area of reaction

2) severity of inflammation

3) inflammation surface involved

4) maximum size of ulceration

5) total area of ulceration

6) area of reaction * severity of inflammation

7) severity of inflammation per surface involved

8) area of reaction * severity of inflammation per surface involved

c) and the two measures of saliva levels:

1) saliva at rest

2) saliva during stimulation

- The major independent variables were:

1) drug group (Bzd or placebo) (DRUG)

2) the number of weeks radiation treatment given (RADWK)

3) the types of radiation (GLAN)

i) high-dose bilateral (both sides of salivary glands)

ii) high-dose unilateral (one side of salivary glands)

iii) low-dose unilateral

The gland field is defined as those salivary glands in the field of radiation. The rest of the independent variables were:

1) sex (male/female)

2) age

3) diagnosis

4) tumor location

5) use of other analgesia:

i) non-narcotic, ii) narcotic, and iii) Xylocaine viscous

6) the factors of time, radiation dose, and fraction (TDF)

7) size of tumor (T-stage)

8) mucosal infection

iii) Preparations for Descriptive Summary

The outcome variables were: the eight measurements of Pain, the eight measures of tissue breakdown (TBD), and the two measurements of saliva levels. These were measured several times for each patient. A preliminary analysis of the data was done using plots and tables to describe and understand the general form of the data.

For the purpose of the analysis, each of these repeatedly measured variables was collapsed into three summary variables: maximum value minus initial value; treatment average value minus initial value; and over-all average value minus initial value, except the variables: burning with drug; taste of drug; analgesia drug; and total drug pain; which were collapsed into the maximum, treatment average, and over-all average values, and the variables: saliva at rest; and saliva during stimulation which were collapsed into the minimum minus initial, treatment average minus initial, and over-all average minus initial values. The collapsed variables measured the presence of extreme conditions (PAIN, TBD and SALIVA).

The initial value is the measurement taken before the treatment is given. The difference from initial value is used to eliminate individual differences, which might have existed prior to the administration of the drug. All comparisons made were based upon the summary variables described above. The SPSSx package was used for this purpose.

iv) The Design of the Experiment

The randomized design experiment was invented by Sir Ronald Fisher in 1920. [Ehrenberg, (1982)]. It has since been extended to more than two experimental groups and provides a routine procedure for reducing prior group differences when comparing drug and placebo effects in a clinical study.

In this clinical situation, randomization procedures were used to balance any possible prior differences between the Bzd and placebo groups except the treatment given. The clinical setting, in which patients were entered into the study as they appeared for treatment, over several months, required that the patients be allocated at random to the treatment groups one at a time. There was no apportunity to confirm that the randomization did achieve balance with respect to the covariate, until the study was under way. Nevertheless, the treatment groups were reasonably well

balanced, as eventually the cross-tabulations were made for the variables of sex, diagnosis, tumor stage, N-stage (size of tumor), tumor location, mucosal infection, and other analgesics (eg., narcotics), in order to compare the Bzd and placebo groups. These cross-tabulations indicated no significant differences between the Bzd and placebo groups.

v) Statistical Inference Technique

Statistical hypothesis tests were applied to the hypothesis concerning the proposed parameters in each model. To provide an interval estimate of a parameter of interest, a confidence interval (C.I.) was constructed. Details of the procedures used for each model are as follows:

1) Cumulative Logit Model

Suppose that the k ordered categories of response have probability $\Pi_{i1}(X)$, $\Pi_{i2}(X)$,..., $\Pi_{ik}(X)$, where i indexes the patient number and the covariates have the value X. In this appplication, k=4, and X is an indicator variable. The dependent variable Y_i is defined to take the values 1, 2, 3, or 4 depending on whether the ith patient's pain is: none, minimal, moderate, or severe. The odds of the event $Y_i \leq j$ is the ratio $\gamma_{ij}/[1-\gamma_{ij}]$

where γ_{ij} is the jth cumulative probability for the ith patient. ie., $\gamma_{ij} = \sum_{k=1}^{j} \Pi_{ik}(X)$, Here, X is the DRUG variable which indicates the appropriate group. Thus the cumulative logit model is written as:

$$\log\left(\frac{\gamma_{ij}}{1-\gamma_{ij}}\right) = \theta_j - \beta X \qquad \text{v.1}$$

From equation v.1 it is clear that the (θ_j) are nuisance parameters in determing the dependence of the odds-ratio on the covariate X. The regression coefficient parameter β is the parameter of major interest which describes how the log-odds are related to the covariates X. It is usual to make an inference concerning this coefficient; the interesting statistical hypothesis is whether or not this coefficient is significantly different from zero.

The estimated values of these unknown parameters were calculated by the methods of maximum likelihood via iterative reweighted least squares (IRLS). The confidence intervals for the regression coefficients were also calculated.

2) Multiple Regression Model

Suppose that each of the eight TBD responses Y has a function g(Y) that is linear in the covariate variables DRUG and RADWK. Then the

multiple regression model is written as follows:

$$g(Y) = \beta_o + \beta_1 DRUG + \beta_2 RADWK + \varepsilon \qquad v.2$$

Where Y represents the eight measures of tissue breakdown (TBD), one at a time and ε is assumed to be normally, independently distributed with zero mean and constant variance σ^2. β_1 is the group effect and β_2 represents the coefficient of the RADWK variable.

For the preliminary analysis, the hypothesis of interest was whether or not the mean of the TBD responses between the two groups (Bzd and placebo) was significantly different beyond the influence of the RADWK variable. Because it was evident that the RADWK variable did not significantly influence the measure of tissue breakdown, we eliminated this variable from the model. Thus, the model remained a one-way ANOVA.

In this case, the null hypothesis of interest was a test whether or not there was a significant mean difference between the Bzd and the placebo groups. More specifically the test is whether the Bzd group was no better than the placebo group. To determine how effective (in reducing the TBD) the Bzd group was compared to the placebo group, we used t-statistics. In this case, high negative values of t-statistics provided evidence against the null

hypothesis, and large positive values of t-statistics indicated that the placebo group was better than the Bzd group. We calculated the estimated values of the means and SE's, and used these to calculate the confidence intervals.

3) One-Way ANOVA Model

Denote the reponse variable SALIVA by Y_{ij}, where Y_{ij} represents the jth patient with the radiation type i. Thus, the one-way ANOVA model is:

$$Y_{ij} = \mu + \alpha_i + \varepsilon_{ij} \quad ; \quad i = 1,2,3 \ \& \ j = 1,2,\ldots,43 \qquad \text{v.3}$$

Here, Y_{ij} are the saliva levels under the two conditions: saliva at rest and saliva during stimulation, α_i is the effect on an observation of the ith type of radiation, and μ is the overall mean.

In this case, the statistical hypothesis test was to determine whether or not there was a significant mean difference between the three types of radiation:

1) high-dose bilateral and high dose unilateral,

2) high-dose bilateral and low-dose unilateral, and

3) high-dose unilateral and low dose unilateral.

Here, the multiple comparisons between these three types of radiation were performed. Again we calculated the estimated values of the means and SE's, to calculate 95% confidence intervals.

4) Multiple Regression Model

To determine whether large amounts of saliva prevent the breakdown of healthy tissue for the two groups (Bzd and placebo), we assumed that the response variables TBD had a mean μ associated with the covariate variables DRUG and SALIVA. Then we fitted the following model to these data:

$$Y = \beta_0 + \beta_1 DRUG + \beta_2 SALIVA + \beta_3 DRUG * SALIVA + \varepsilon \qquad v.4$$

Where ε is assumed to be normal, independently distributed with zero mean and constant variance σ^2. DRUG is the dummy variable for the two groups and the variable SALIVA represents the two different conditions of saliva levels (one at a time).

The statistical hypothesis test indicated whether or not the regression coefficients β_2 and β_3 were significantly different

from zero. In other words, it tested whether the SALIVA variable had a significant influence on the eight TBD responses beyond the influence evident from the DRUG variable. A least squares method was used to obtain the estimated values and SE values.

vi) Method of Estimation

The maximum likelihood via the iterative reweighted least squares method was applied for the purpose of estimating the parameters of the cumulative logit model. A standard least squares method was used for the one-way ANOVA and multiple regression models, but as this is standard it does not merit further discussion here.

For this project, to estimate the unknown parameter vector β in the cumulative logit model, we solved the maximum likelihood equation. The algorithm commonly used in the BMDP3R program (from the biomedical computer program, BMDP, at the University of California) is the Gauss-Newton algorithm which is usually employed in non-linear regression parameter estimation. In addition to this, the parameter estimation procedures for the Generalized linear model (GLM) were introduced (see appendix-A for more details). Here, two possible approaches were to apply the model in the GLIM (Generalized Linear Interactive Model) program or in the BMDP3R program. Unfortunately the model does not work in

GLIM directly, and a GLM macro would have had to be written to do the iterative algorithm. For this reason a modification of the BMDP3R program was chosen as the easiest way to find the maximum likelihood estimate (MLE).

- Iteratively Reweighted Least Squares (BMDP3R)

If we define the equation (v.1) in the Section II(v). in the form:

$$Y_{ij} = f(\theta_j, \beta, X_i) + \varepsilon_{ij} \qquad (1)$$

Where $f(\theta_j, \beta_i, X) = n_i [\gamma_{ij} - \gamma_{ij-1}]$ and

$$\gamma_{ij} = \frac{1}{1+\exp(-\theta_j + \beta X_i)}$$

with weight $W_{ij} = 1 / f(\theta_j, \beta, X_i)$

then the unknown parameters θ_j and β are estimated by minimizing the residual sum of square RSS which is:

$$RSS = \sum\sum [W_{ij}(\theta_j, \beta, X_i)] * [Y_{ij} - f(\theta_j, \beta, X_i)]^2 \qquad (2)$$

Since the weight W depends upon the parameters θ_j and β, and the function f(*) is non linear in the parameters, we cannot minimize

RSS directly, so we use the Gauss-Newton algorithm.

If we write the non-linear model (1) in terms of a linear approximation by Taylor series expansion at initial values as:

$$f(\Theta_j) \cong f(\Theta^\circ_j) + \frac{\partial f(\Theta_j)}{\partial \theta_1}\Big|_{\theta_1=\theta^\circ_1,\theta_2=\theta^\circ_2,\theta_3=\theta^\circ_3,\beta=\beta^\circ} * (\theta_1 - \theta^\circ_1)$$

$$+ \frac{\partial f(\Theta_j)}{\partial \theta_2}\Big|_{\theta_1=\theta^\circ_1,\theta_2=\theta^\circ_2,\theta_3=\theta^\circ_3,\beta=\beta^\circ} * (\theta_2 - \theta^\circ_2)$$

$$+ \frac{\partial f(\Theta_j)}{\partial \theta_3}\Big|_{\theta_1=\theta^\circ_1,\theta_2=\theta^\circ_2,\theta_3=\theta^\circ_3,\beta=\beta^\circ} * (\theta_3 - \theta^\circ_3)$$

$$+ \frac{\partial f(\Theta_j)}{\partial \beta}\Big|_{\theta_1=\theta^\circ_1,\theta_2=\theta^\circ_2,\theta_3=\theta^\circ_3,\beta=\beta^\circ} * (\beta - \beta^\circ)$$

where, $f(\Theta_j) = f(\theta_1,\theta_2,\theta_3,\beta)$

Let $\beta = \theta_4$, then the above equation could be written as :

$$f(\Theta) \cong f(\Theta^\circ) + \sum_{k=1}^{4} \frac{\partial f(\Theta)}{\partial \theta_k}\Big|_{\Theta=\Theta^\circ} * (\theta_k - \theta^\circ_k) \qquad (3)$$

Where, Θ°= a column vector of initial values of the parameters: θ_1, θ_2, θ_3, β (or θ_4).

Now let $Y^\circ_{ij} \cong Y_{ij} - f(\Theta^\circ)$ where, Y° is 2x4 matrix (4)

then $$Y^\circ_{ij} \cong \sum \frac{\partial f(\Theta)}{\partial \theta_k}\Big|_{\Theta=\Theta^\circ} * (\theta - \theta^\circ_k) + \varepsilon_{ij} \qquad (5)$$

let D° be a 2x4 matrix whose (i,j) entry is $\left.\frac{\partial f(\Theta_j)}{\partial \theta_j}\right|_{\Theta=\delta}$

and $\Delta^{\circ} = [\ \theta_1-\theta_1^{\circ},\ \theta_2-\theta_2^{\circ},\ \theta_3-\theta_3^{\circ},\ \beta-\beta^{\circ}]^{T}$

$$= \Theta - \Theta^{\circ} \qquad (6)$$

Here equation (5) could be written as follows:

$$Y^{\circ} \cong D^{\circ}\Delta^{\circ} + \varepsilon^{\circ} \qquad (7)$$

with $E(\varepsilon) = 0$ and $cov(\varepsilon) = W^{-1}$

Now to get the estimated values of the parameters we apply the ordinary least square method to the equation (7) as follows: multiplying (7) by $W^{\circ 1/2}$ we get

$$[W^{\circ}]^{1/2}Y^{\circ} = [W^{\circ}]^{1/2}D^{\circ}\Delta^{\circ} + [W^{\circ}]^{1/2}\varepsilon^{\circ}$$

$$Z^{\circ} = U^{\circ}\Delta^{\circ} + E^{\circ} \qquad (8)$$

where, $Z = [W^{\circ}]^{1/2}Y$, $U = [W^{\circ}]^{1/2}D^{\circ}$ and $E = [W^{\circ}]^{1/2}\varepsilon$,

with $E(E) = 0$ and $V(E) = I$.

So $$\hat{\Delta}^{\circ} = (U^{\circ T}\ U^{\circ})^{-1}U^{\circ}\ Z^{\circ}$$

where $\hat{\Delta}^{\circ}$ is an estimate of $(\Theta-\Theta^{\circ})$, and by substituting the original value Y we get:

$$\hat{\Delta}^{\circ} = (D^{\circ T} W^{\circ} D^{\circ})^{-1} (D^{\circ} W^{\circ} Y^{\circ}) \qquad (9)$$

By evaluating the equation (9), the estimated parameters of the linear terms of the Taylor series expansion of the non-linear model are obtained from the equation:

$$\hat{\Theta} = \hat{\Theta}^{\circ} + \hat{\Delta}^{\circ} \qquad (10)$$

Thus, by giving the initial values we could obtain the weight, W, and then substitute the values in the equation (9). By inserting these values consecutively into the subsequent equation (10), we obtain the new estimated values of the non-linear model. These iterations continue until the solution converges, that is, until in successive iterations $\hat{\Theta}^{\alpha+1} \cong \hat{\Theta}^{\alpha}$ or

$$| \hat{\Theta}^{\alpha+1} - \hat{\Theta}^{\alpha} / \hat{\Theta}^{\alpha} | < \delta$$

where δ is some pre-specified amount [e.g.,0.000001]. The RSS can be evaluated at each stage of the iterative procedure to see if a reduction in its value has in fact been achieved. In other words, the above procedures are repeated continually until the sequence of estimates converges, or if the sequence does not converge, a new set of initial values must be tried.

vii) Statistical Software

This section will briefly discuss the choices of different software used in the subsequent analyses: BMDP3R; GLIM; SPSSx; and MINITAB.

The BMDP3R program was chosen to estimate the parameters of the non-linear regression model. This program was convenient to use to obtain the desired estimate of the parameters of the cumulative logit model, since one merely needs to supply the derivatives of the expected value of the roughly estimated density function to form the new design matrix at each iteration. To do so, the program minimizes the residual sum of square RSS of a non-linear regression model. The program's default stopping rule is then based on the change of the RSS (see the BMDP-manual for more detail). However, because of the weight variation from one step to another, the MLE $\hat{\beta}$ does not correspond to the smallest possible value of the RSS. Therefore, the program must be told not to monitor the RSS in order to decide when to stop iterating. This could be managed by giving additional commands in the regression section of the program: by setting the convergence to minus one, by specifying the number of iterations desired, and by setting the permissible number of halvings to be zero. For the same reasons any partial step modifications which monitor RSS should be turned

off. To do so in the P3R program, we need to set the maximum number of step halvings to zero.

The GLIM (Generlized Linear Interactive Model) program was chosen to do the regression analysis as well as the one-way ANOVA techniques. This GLIM program was easy to use and it provided the variance-covariance of the difference between the slopes coefficients for each pair of groups. The SPSSx (Statistical Package for Social Science) program was used to manipulate the data and to calculate the three collapsed variables for each measurement of the pain,tissue breakdown, and SALIVA variables. The MINITAB source file was also used in the description of the data, and for the construction of tables.

III. MODEL APPLICATION TECHNIQUES

i) Preparation of the Data for Analysis

The variables were specifically defined and summarized for the proposed models. Initial data manipulation was carried out to assemble the data in a form suitable for analysis. For the independent variables, ie. the drug group and the radiation type, "dummy" variables were created. The eight PAIN responses were combined into four categories and treated as ordinal response variables.

For the first objective, the eight visual analog scales measurements of pain were considered as ordinal responses and the DRUG group as an independent variable for the cumulative logit model; The second objective, the eight tissue breakdown variables were considered as the response variables and the DRUG group and RADWK as independent variables for the multiple regression model; The third objective, the two levels of saliva (saliva at rest and saliva during stimulation) were considered as the response variables and the three types of radiation as independent variables for a one-way ANOVA model; and finally, the eight tissue breakdown were individually represented as response variables, and

each of the two saliva levels and the DRUG group were represented as independent variables for the multiple regression models.

ii) Choice of Model & Link Function

Different link functions for various models were examined for the purpose of fitting the data. The modelling was done separately for each objective.

1) Objective 1: Cumulative Logit Model

Several statistical models have been suggested as being appropriate for use with ordinal response variables. These have been classified into two types, depending on whether or not the model is invariant under the grouping of adjacent response categories [McCullagh and Nelder (1983)]. If a new category was formed by combining adjacent groups on the previous scale, the form of the conclusion should be unaffected. However, in this way some information will be reduced.

Hence, these considerations led to models based on the cumulative distribution probability, and not to an individual probability for the response categories themselves.

To reflect the ordinality of the response variable one possible model is the cumulative logit model:

$$\log\left(\frac{\gamma_{ij}}{1-\gamma_{ij}}\right) = \theta_j - \beta X \qquad \text{III.2.1}$$

We may note that the interpretation of β does not depend on the particular choice of categories if II.2.1 is true. For this project the above statement was used for four categories of pain levels.

Now, to determine the effects of Bzd on the eight ordinal pain responses, the two treatment groups were compared using the odds ratio.

If we define γ_{ij} as the probability of a patient of group i falling into the first j categories, then $\frac{\gamma_{1j}}{1-\gamma_{1j}}$ represents the odds of the Bzd group falling into the first j categories, and the corresponding odds for the placebo group are $\frac{\gamma_{2j}}{1-\gamma_{2j}}$. Here X is an indicator variable and the regression coefficient β is the parameter of interest.

Thus, $\log\left(\frac{\gamma_{1j}}{1-\gamma_{1j}}\right) = \theta_j - \beta$

and $\log\left(\frac{\gamma_{2j}}{1-\gamma_{2j}}\right) = \theta_j$

then $\frac{\gamma_{1j}}{1-\gamma_{1j}} = \exp(\theta_j - \beta)$

$$\frac{\gamma_{2j}}{1-\gamma_{2j}} = \exp(\theta_j)$$

Thus, the odds-ratio is given by $\exp(-\beta)$. However, since our estimates are logistic contrasts with the placebo group, a high positive value of β represents a tendency towards the more severe pain categories relative to the placebo group, and a large negative value indicates the reverse.

Note that when there are only two response categories (k=2), equation II.2.1 above is equivalent to the logistic model for binary data [Cox (1970)], and in this particular case it is also equivalent to a log-linear model. In general however, when the number of categories exceeds two, the logit model II.2.1 does not correspond to a log-linear structure. J. A. Anderson warned in P. McCullagh's paper (1980), that special attention must be given to the number of parameters before fitting the cumulative logit model. As the number of parameters increases, the chance of the sparse data problem occurring also increases.

2) Objective 2: Multiple Regression Model

The multiple regression technique was applied in ascertaining whether or not there was a significant mean difference between

the Bzd and placebo groups after taking into account the effect due to the different RADWK distributions. This procedure is a combination of the analysis of variance and the regression analysis, usually called analysis of covariance.

To determine the effect of Bzd treatment on the eight tissue breakdown variables, different transformations of the dependent variables were examined (eg. square root, inverse, logarithmic, identity etc.) for the purpose of fitting the data. The residual plot was used for checking the appropriateness of the models.

3) Objective 3: One-Way ANOVA Model

Analysis of variance is a technique useful in determining whether or not there are significant mean differences between the groups. The ANOVA model would be appropriate to apply in a situation where we wish to determine whether or not there are significant differences in the amount of saliva among the groups determined by the type of radiation used. The dependent variable here was the amount of saliva and the independent variable was the radiation type. The above description is referred to as a one-way ANOVA model since only one independent variable (radiation type) is employed.

The ANOVA model can take on two main forms, the fixed-effects model and the random-effects model. The fixed-effects model is more appropriate than the random-effects model since the treatment level or groups of each independent variable, from which one takes a sample of population units, is exhaustive of all groups of interest to the investigator.

The ANOVA model maximizes the between-to-within group sum of squares in order to reject the null hypothesis of equal group means. In the fixed-effects model, the null hypothesis (H_o) is used to test for the acceptance or rejection of the equality of the group means. In this project the null hypothesis H_o was the three types of radiation have equal means. This hypothesis is tested against the pre-selected significance level. The test statistic that ANOVA uses to test H_o is the F-ratio. Generally, a large F-ratio implies that the null hypothesis of equal means is rejected (ie. there are significant differences among the mean values of the radiation type). H_o is correctly rejected if the computed F-ratio exceeds the critical F-statistic found in an appropriate table of a pre-specified significance level.

4) Objective 4: Multiple Regression Model

Multiple regression analysis is a general statistical technique

used to determine the relationship between the single response variable and several indpendent variables. For the purpose of predicting the extent of tissue breakdown from the amount of saliva for the two treatment groups (Bzd and placebo), a multiple linear model was fitted to the data.

iii) Transformations

Most statistical analyses are based on certain assumptions. To make these assumptions as valid as possible, it may be necessary to transform the original data. Transformations which serve to make the data more symmetrically distributed usually simplify the analysis, interpretation and presentation. Transformation to normality are commonly sought. However, a more frequent problem than non-normality is the fact that the different groups of values have varying degrees of spread. This problem makes the comparison of measures of location very difficult. To promote homogeneity of variance, some of the original data were necessarily transformed.

v) Residual analysis

For diagnostic procedures, checking the adequacy of the models is carried out not only for linear regression but also for any fitted

models such as ANOVA, cumulative logit models and so forth. In this study, we have attempted to develop appropriate models for each specific data set.

The residual analysis technique is used for checking the adequacy of fitted models. In general, the goal in the study of the residuals is to check the assumptions concerning the error term ε. In regression models, the usual assumption is that the errors are independent and normally distributed with a mean of zero and constant variance, σ^2.

In this case, since the residuals, $\hat{Y} - Y$, and the corresponding fitted values $\hat{Y}$ are independent, a plot of the residuals versus the fitted value $\hat{Y}$ was used as the main tool in fitting the appropriate models. This plot helped to indicate whether or not the model was a good fit over the whole range of the data. It also helped to indicate the constancy of variance.

The residuals were calculated from the discrepancies between the observed values Y and the corresponding fitted values $\hat{Y}$. It is the measurement of the vertical distance between the point and the line which expresses the best fit for the data. Mathematically this can be written as:

$$e_i = Y_i - \hat{Y}_i \qquad i = 1,2,\ldots,n$$

where e is considered as the observed error. If the proposed model is appropriate, the residuals should not display any obvious trend. By plotting the residuals, we have an informed graphical test of the model.

IV. RESULTS

1) Application of Models to the Data Set

To answer Dr. Epstein's four major objectives, (see p.2), we chose models appropriate to the relevant data sets described in Tables 1 to 4. These tables, and the application of the specific models, are outlined below:

(a): The data set in Table 1.1 consists of: the eight symptoms of pain recorded using the visual analog scales (VAS) and treated as ordinal response variables; and the DRUG group treated as an independent variable. Each of these responses were combined into four categories (see Table 1.2) as follows :

1. none 2. minimal 3. moderate 4. severe

The cumulative logit model was chosen for these data.

(b): The data set in Table 2 consists of: the eight tissue breakdown (TBD measurements (A1, A2,...A8) treated as response variables; and DRUG and RADWK treated as independent variables. (RADWK is the number of weeks patients received radiation

therapy.) In this situation, some original response variables were transformed by the square root: the area of reaction, the area of reaction * severity of inflammation and the area of reaction * severity of inflammation per surface involved; while other variables: the maximum size of ulceration, and the total area of ulceration, were transformed by the logarithmic function. The standard regression model was fitted to the transformed data.

(c): The data set in Table 3 consists of: the two conditions of saliva levels expressed as response variables - the amount of saliva at rest and during stimulation; and the three types of radiation treatment (high dose bilateral, high dose unilateral, low dose) expressed as independent variables. The one-way ANOVA model was applied to the given data. (As is discussed later, the DRUG variable was not a determinant of saliva levels.)

(d): The data set in Table 4 consists of: the eight tissue breakdown response variables, considered here as dependent variables; the saliva level under two conditions, while at rest and during stimulation, as independent variables; and the DRUG group variable also as an independent variable. The multiple regression technique was found to be appropriate for this data.

2) Descriptive Summary

The total sample size was 43 patients, broken down into two groups: the Bzd group included 25 patients, 14 men and 11 women, with a mean age of 62 years (range, 39 to 80 years and SD=11.2). The control group included 18 patients, 9 men and 9 women, with a mean age of 54 years (range, 26 to 76 years and SD=12.8). The RADWK variable represents the number of weeks that radiation therapy was received. The weeks of radiation therapy for the two groups are displayed in Table 5. The measurements of the pain, TBD and SALIVA levels were also taken at weekly intervals. For each of these outcome variables, the raw (time-collapsed) data and the tables of mean ± SE are displayed in Table 6 and Table 7 respectively. (The means of the measurements of PAIN, portion of Table 7 must be interpreted with caution since the measurement of pain are ordinal.)

Since the data was collected for each patient at weekly intervals, the mean ± SE of each measured variable in the Bzd group was plotted versus the time (weeks). See Figures 1.1 to Fig. 3.2. This was repeated for the corresponding placebo group. In this way we were able to visually compare time trends in the two groups. In other words, we were able to observe any reduction of pain, tissue breakdown, and saliva, over a period of time.

We can now examine the pain data of Table 8 (which are summarized in Table 1.) To determine the efficacy of Bzd on perceived pain reduction, the original data were measured through the VAS, ie., patients recorded their pain on a scale of 0 to 10, where 0 means no pain and 10 maximum pain. Since the measurements of the pain were taken at weekly intervals, the two groups were examined to see during which weeks they were significantly different. In other words, aside from observing any differences during the over-all period of treatment, we also looked at whether or not the two groups were remarkably different at specific times during the treatment. The results of these observations also indicated that the two groups showed little difference in pain reduction. Because of the nature of the data and technical problems as described below, we combined each variable into first four and later three categories, but even with this aggregated data, the visual impression was the same.

The following comments relate to Table 9, which shows the weekly measurements of the tissue breakdown variables. These measurements, which represent the extreme condition of breakdown of healthy tissue, were summarized in Table 2 by calculating the maximum value minus the initial value. The mean ± SE of each measurement of the tissue breakdown were displayed in Table 7. In order to visualize, over time, Bzd's efficacy for the reduction of tissue breakdown, the mean and SE were plotted versus the time

(weeks) [see figure Fig 2.1 to Fig 2.5.]

The following comments relate to the data summarized in Table 3. The three types of radiation were pre-selected by the investigator whose question of interest was whether or not the type of radiation affects the amount of saliva. Table 3, which is the summary of Table 10, represents the difference between the minimum values minus the inital value. This summary table measures the negative effects of the radiation treatment. The mean ± SE are displayed in Table 7 and the plot of the means and SE's versus the time (weeks) are in Fig 3.1 to F3.2.

Table 4 was set in order to determine whether an increased amount of saliva was associated with a reduction in the tissue breakdown. This table takes its data from Tables 2 and 3: the measurements of tissue breakdown and SALIVA for the Bzd and placebo groups.

3) Parameter Estimates and Their Interpretation

The results of the application of the cumulative logit model to the pain variables, the analysis of variance model to the SALIVA level variables, and the regression analysis on the TBD variables are given under the model headings below.

i) Objective 1: Cumulative Logit Model

To determine the efficacy of the Bzd treatment on perceived pain reduction, the cumulative logit model [McCullagh & Nelder 1983) was applied to analyze the data. In particular, this model is appropriate for ordinal response categories.

To determine the effects of Bzd on the eight measurements of pain, the ordinal responses which were classified into four categories, we compared the two groups of treatment in terms of the odds-ratio. The odds-ratio is given by $\exp(-\beta)$. However, since our estimates are logistic contrasts with the placebo group, a high positive value of β represents a tendency for responses in the treatment group to be shifted towards the severity categories relative to the placebo group, and a large negative value indicates the reverse.

The results of these analyses indicate that all the pain variables recorded a negative value of the β coefficient except the coefficients of the taste-of-drug and analgesia-drug variables. Although these statistical results indicate that the Bzd group has no significant effect, there is a trend which indicates the Bzd group tends to show reduction of pain by the factors: 1.33, 1.35, 2.66, 2.40, 1.17, and 1.30 for the variables:

burning at rest, burning with eating, pain at rest, pain with eating, and burning with drug, and over-all drug pain respectively. While the taste of drug and analgesia drug variables tend to be the reverse with factors of 0.6 and 0.4 respectively. The results of these analysis are displayed in the following table:

The measurements of PAIN; a negative value of β indicates a reduction of PAIN.

VARIABLE NAME OF PAIN	ESTIMATED VALUE OF β	SE (β)	P-VALUE	95% C.I OF β
Burning at rest	-0.282	0.555	0.31	(-1.37,0.81)
Burning with eating	-0.299	0.555	0.30	(-1.39,0.79)
Pain at rest	-0.977	0.585	0.08	(-2.14,0.19)
Pain with eating	-0.875	0.577	0.09	(-2.00,0.26)
Burning with drug	-0.161	0.556	0.39	(-1.25,0.93)
Taste of drug	0.512	0.619	0.22	(0.70,-1.72)
Analgesia drug	0.917	0.597	0.09	(0.26,-2.09)
Over-all drug pain	-0.268	0.588	0.33	(-1.42,0.88)

The Bzd treatment does not appear to be very effective in reducing pain. At a 5% level of significance, none of the variables is significant. That is, the data are consistent with a range of β values which includes the null value β=0. Based on these analyses the evidence for the beneficial effects of the Bzd

treatment is weak. In other words, for patients in the Bzd group or in the placebo group, the effectiveness of the treatment on pain reduction was the same. A combined test of significance was not done but may have been shown Bzd to be significant in its effect on pain.

ii) Objective 2: Multiple Regression Model

In order to determine whether or not the mean of these tissue breakdown variables for the two groups differed significantly after taking into account the effects due to the different RADWK distributions, a multiple regression technique was used. The results of the tissue breakdown responses reveal that the RADWK variables have insignificant influence beyond the influence evident from the DRUG group. The RADWK variable was therefore eliminated from the model, the remaining model being equivalent to a one-way ANOVA.

Based on the reduced model, the mean differences between the two treatment groups seem to be highly significant for the following variables: area of reaction, maximum size of ulceration, total area of ulceration, area of reaction * severity of inflammation, and area of reaction * severity of inflammation per surface involved, with the p-values: 0.017, 0.017, 0.009, 0.030,

0.018 respectively. While the variables: severity of inflammation, total inflammation surface, and severity of inflammation per surface involved, were not significant with the p-values: 0.06, 0.165, 0.600 respectively.

The measurements of tissue breakdown (TBD); the negative value of β indicates that the Bzd group tends to reduce TBD relative to the placebo group.

VARIABLE NAME OF TBD	ESTIMATED VALUE (β)	SE(β_1)	P-VALUE	95 % C.I OF (β)
Area of reaction	-17.72	8.24	0.017	(-34,-1.60)
Severity of inflammation	-1.83	1.28	0.068	(-4.4,0.70)
Total inflammation surface involved	-0.44	0.49	0.165	(-1.4,0.50)
Maximum size of ulceration	-2.04	0.94	0.017	(-3.9,-2.0)
Total area of ulceration	-7.24	2.63	0.009	(-12.4,2.0)
Area of reaction * severity of inflammation	-308.60	164.90	0.030	(-629,-19)
Severity of inflammation per surface involved	-0.93	1.40	0.600	(-3.7,2.0)
Area of reaction * severity of inflammation per surface involved	-49.00	23.38	0.018	(-3.0,-95)

Since the DRUG group was an indicator variable, it was defined as 1 for the Bzd and 0 for the placebo group. Thus, a high negative value of the t-statistics indicated that the Bzd group tended to reduce the tissue breakdown relative to the placebo group, and the positive value of the t-statistics indicated the reverse. See the above table for the estimated values and the relevant SE-values.

iii) Objective 3: One-Way ANOVA Model

Here, the objective was to determine the effects of radiation type on the two conditions of saliva levels: while at rest and during stimulation. To do so, the three types of radiation were tested for a significant mean difference at each condition of saliva levels. The results of these analyses were tested by an F-test, which indicated that the null-hypothesis concerning the equality of the means was rejected with the p-values 0.05 and 0.0004 respectively. That is, the three types of radiation had a significant mean difference on the two saliva levels. The results of these analyses are displayed in the following table:

The measurements of saliva levels

VARIABLE NAME	F-VALUE	P-VALUE
saliva level while resting	2.955	0.05
saliva level during stimulation	10.002	0.0004

iv) Objective 4: Multiple Regression Model

In the preliminary analysis, we fitted the regression model without the interaction term; it indicated that the saliva coefficient was not significantly different from zero. Later, we introduced the interaction term as shown in the above equation v.4, in Section II which reasonably fitted the data well.

The objective was to determine whether increased amounts of saliva prevent the breakdown of healthy tissue in the two groups. A negative value of the SALIVA coefficient β_2 with high t-statistics was evidence that the variable of SALIVA helped to predict the reduction of the tissue breakdown variables for the placebo group, while a positive value of β_2 indicated the reverse.

Similarly the sum of the coefficients β_2 and β_3 with high negative t-statistics was also evidence for the Bzd group. Based on this model we might draw the following conclusion: the SALIVA variable during stimulation was not significant to predict the tissue breakdown variables. But there is a tendency that an increased amount of saliva while at rest did reduce the tissue breakdown for the placebo group. This could be seen in table below, that a significant negative coefficient of β_2. Furthermore, the significant negative value of sum of β_2 and β_3, indicates the reduction tissue breakdown for an increased amount of the saliva while at rest for the Bzd group.

However, having a significant negative coefficient of saliva while at rest (for placebo group) were the variables: the area of reaction, total area of ulceration, area of reaction * severity of reaction, and area of reaction * severity of inflammation per surface involved, with p-value: 0.001, 0.008, 0.003, 0.001 respectively. The regression results of estimated values, along with the SE values are displayed in the following table:

The association of TBD with SALIVA variable.

VARIABLE NAME OF TBD	ESTIMATED VALUES OF $\hat{\beta}_2 \pm SE(\hat{\beta}_2)$	$\hat{\beta}_3 \pm SE(\hat{\beta}_3)$
Area of reaction	-6.15±1.98	7.55±2.93
Severity of inflammation	-0.42±0.31	0.98±0.46
Total inflammation surface involved	-0.03±0.13	0.25±0.19
Maximum size of ulceration	-0.22±0.25	0.39±0.37
Total area of ulceration	-1.58±0.63	2.37±0.93
Area of reaction * severity of inflammation	-117.56±40.3	142.54±59.7
Severity of inflammation per surface involved	-0.07±0.11	0.15±0.16
Area of reaction * severity of inflammation per surface involved	- 17.63±5.62	21.22±8.32

4) Scientific Conclusions

The major objective of Dr. Epstein's study was to determine the efficacy of the drug Benzydamine (Bzd) on perceived pain reduction, and thereby determine the effectiveness of the drug in the management of the mucositis among patients undergoing radiation therapy. The secondary objective related to the drug's potential usefulness in the treatment of other causes of oral tissue breakdown (ie. chemotherapy, trauma, infection, etc.) .

Dr. Epstein's patients frequently reported pain as the first symptom alerting them to the need for professional care. Although the results of these analyses indicated that the patients who rinsed with Bzd tended to have less burning at rest, burning with eating, pain at rest, pain with eating, burning with drug, taste of drug and overall pain than patients using the placebo, nevertheless statistically the differences were not significant. In other words, the two groups of patients (those receiving Bzd and those receiving the placebo rinse) exhibited no significant differences in their perceptions of pain. Since all patients reported increased pain during the study, all required symptom management. Dr. Epstein reported that the placebo group began systemic medications earlier in the course of radiation therapy than did the Bzd group. While there were no significant

differences in the use of systemic analgesics, a trend to lessen the use of narcotic analgesics was indicated in the Bzd group. (See Section IV, iii for details.)

In this study, Bzd was studied as a prophylactic rinse. Beginning when radiation was initiated, a statistically significant reduction in mucositis was demonstrated. That is, Bzd tended to be superior to a placebo rinse in reducing mucositis during the radiation therapy. Dr. Epstein pointed out that assessment of mucositis is affected by the fact that in radiation therapy, the field size is directly related to the area of reaction. This limited the use of the total area of reaction as a factor in the assessment of mucositis. The most useful factors were the maximum size of ulceration and the total area of ulceration. The findings of clinical evidence of reduction in inflammation and ulceration of oral mucosa suggest that Bzd can be used as an oral rinse to prevent mucositis. In other causes of mucositis, for example, chemotherapy, the total area of reaction may be of greater importance as a measure of the severity of tissue damage. The severity of tissue breakdown was graded by the size of the area of involvement, maximum size of ulceration, and total area of ulceration for each surface of the oral cavity involved. Each of these variables was assessed separately. In order to assess the severity of reaction and to weight the degree of inflammation as an important variable, the inflammation score

was multiplied with the other variables to provide a combined score for mucositis that was more representative of the severity of tissue reaction.

Moreover, each patient was given one of the three types of radiation: high dose bilateral, high dose unilateral, or low dose. The amounts of saliva level at two conditions (while at rest and during stimulation) were measured. The statistical results of these analyses reveal that the three types of radiation have a significant mean difference in their effects on salivation, whether or not the measurement of saliva was taken under stimulation. In particular, patients who received a high dose bilateral seemed to produce more saliva than those who had only high dose unilateral or low dose.

Finally, the patients in the two groups who had large amounts of saliva at rest tended to have less tissue breakdown. In particular, an increase in the amount of saliva tended to reduce the area of reaction, total area of ulceration, area of reaction * severity of inflammation, and the area of reaction * severity of inflammation per surface involved.

V. DISCUSSION

The purpose of this section is to provide further details concerning issues that may bear on the appropriateness of the analytical methods and the conditions. Major problems in the experiment as well as the technical problems in its analysis are explained. Specific attention will be paid to missing values.

Forty-three patients completed Dr. Epstein's clinical study. Compliance was a greater problem in the placebo group: six patients dropped out of the study. One possible explanation of this would be that the lack of compliance was a result of the lack of the therapeutic effect of the placebo rinse. This would be in accord with the finding on the complying patients.

During the clinical study, Dr. Epstein reported that pain and discomfort often reached a maximum some time during the last one or two weeks of therapy, and did not continue to increase in severity. He suggested that this may indicate that as treatment progressed, the patients became more tolerant of the pain because the maximum tissue reaction had already occurred, and/or altered neurologic functioning developed due to the direct effects of radiation on the nerves. This may explain why the apparent

advantages for pain reduction of the Bzd over the placebo failed to be statistically significant.

Technical problems arose in attempting to organize the data and in fitting the appropriate models. One problem was that some of the consenting patients missed a number of regular measurements for a variety of reasons, and these missing records led to unequal information from the patients, causing problems for analysis . The number of missing values of each measurement of pain, tissue breakdown, SALIVA in each week are displayed in Table 9.

To overcome this difficulty we studied the behaviour of the data visually and summarized this information into three collapsed variables: maximum minus initial values, treatment average minus initial values, and over all average minus initial values. In the case of the two conditions of saliva we used minimum instead of maximum values, and for the variables: burning with drug; taste of drug; analgesia drug; and total pain of drug, we used the maximum values, the treatment average values, and the overall average values. The subtraction of initial value was used to eliminate individual differences prior to the administration of the drug. These collapsed variables measured the presence of extreme conditions (pain, saliva, tissue breakdown). The conclusions were similar no matter what response variable was used. We reported only on the use of maximum minus the initial values of each

measurement of tissue breakdown and pain (except for the variables: burning with drug; taste of drug; analgesia drug; and total pain, where the maximum values were reported), while the minimum minus initial values were reported in the case of the saliva levels.

In fitting the cumulative logit model in the BMDP3R program, one of the major problems was to provide the initial values for the required parameter estimations. However, by guessing at reasonable initial values, it was possible to achieve convergence after a few iterations. Dr. J. A. Anderson commented in McCullagh's paper (1980) that in fitting the cumulative logit model, one should notice that, as the number of parameters increases, the chance of the sparse data problem occurring also increases. This may explain why the model with ten categories fails to converge.

TABLE 1 *The eight measurements of PAIN (V1 TO V8):*

1.1 The possible explanatory variable is DRUG group (GP)

V1 to V4 *were measured by maximum minus initial values*

V5 to V8 *were measured by maximum value*

GP	V1	V2	V3	V4	V5	V6	V7	V8
1	8	8	7	7	4	4	5	5
1	0	0	3	3	0	3	1	0
1	7	8	6	8	9	9	5	5
1	0	3	0	3	5	5	0	3
1	0	4	0	5	2	4	5	2
1	6	5	6	6	0	2	2	2
1	2	0	0	0	0	5	0	3
1	5	5	5	5	2	5	2	5
1	1	1	0	0	2	3	5	4
1	0	1	0	0	2	2	2	3
1	3	5	0	2	2	2	3	2
1	8	10	5	7	5	3	2	4
1	6	7	3	0	3	4	3	4
1	2	2	1	0	5	0	1	1
1	8	7	0	0	10	7	8	8
1	0	0	0	0	0	3	2	2
1	0	5	0	0	2	0	0	2
1	4	4	2	5	2	1	3	1
1	5	8	1	8	0	0	1	1
1	0	0	0	0	1	2	3	3
1	2	2	0	5	5	2	2	2
1	4	2	5	5	5	3	0	4
1	8	6	5	6	10	3	2	1
1	10	10	10	10	10	2	2	10
1	1	4	1	1	2	3	2	2
2	4	1	5	4	0	0	0	0
2	4	6	4	5	5	3	5	5
2	5	0	3	7	5	5	5	5
2	4	8	8	9	3	0	2	3
2	2	5	2	5	2	5	5	5
2	1	5	0	2	1	4	3	2
2	4	1	7	6	7	2	4	3
2	8	9	8	8	2	7	4	6
2	7	7	0	0	0	3	0	7
2	5	9	0	0	10	2	1	2
2	5	7	6	6	10	4	0	9
2	9	9	8	9	10	1	0	1
2	1	1	0	0	0	1	2	1
2	0	0	0	1	2	2	0	4
2	4	2	5	5	5	3	0	4
2	9	9	8	9	10	2	0	2
2	7	8	7	8	2	1	1	1
2	0	0	0	5	1	2	1	2

NOTATION

GP= *Drug (Bzd / Placebo)*
V1 = *Burning at rest*
V2= *Burning with eating*
V3= *Pain at rest*
V4= *Pain with eating*
V5= *Burning with drug*
V6= *Taste of drug*
V7= *Analgesia drug*
V8= *Total Pain of drug*

TABLE 1 *The eight measurements of PAIN*

1.2 The aggregated four categories of PAIN:

1. none 2. minimal 3. moderate 4. severe

PAIN	GROUP	1	2	3	4	N
V1	D	9	6	5	5	25
	P	4	6	5	3	18
V2	D	6	7	7	5	25
	P	6	1	5	6	18
V3	D	14	3	7	1	25
	P	6	3	5	4	18
V4	D	10	3	9	3	25
	P	4	2	7	5	18
V5	D	6	10	5	4	25
	P	5	5	4	4	18
V6	D	4	16	4	1	25
	P	5	10	3	0	18
V7	D	7	13	4	1	25
	P	10	5	3	0	18
V8	D	5	15	3	2	25
	P	4	8	5	1	18

TABLE 2 *The eight measurements of Tissue Breakdown (A1 to A8);*

The possible explanatory variables:

Drug group (GP), Radiation weeks (R), TBD are sorted by R

GP	R	A1	A2	A3	A4	A5	A6	A7	A8
1	2	6	4	4	1	1	24	1	6
1	3	22	6	3	9	14	132	2	44
1	3	13	7	4	3	7	91	2	23
1	3	25	10	5	3	8	250	2	50
1	3	19	11	5	3	12	209	2	42
1	3	20	6	3	8	14	120	2	40
1	3	40	16	8	2	20	640	2	80
1	3	25	6	3	2	8	153	2	51
1	3	11	12	3	2	9	132	4	44
1	3	6	6	3	1	1	36	2	12
1	3	10	8	3	2	6	80	3	27
1	4	13	3	2	1	1	39	1	19
1	4	8	10	5	1	2	80	2	16
1	5	3	2	1	1	1	6	2	6
1	5	22	10	5	1	10	220	2	44
1	5	8	5	4	1	2	40	1	10
1	5	17	10	5	1	7	170	2	34
1	5	25	7	4	1	9	175	2	44
1	5	7	4	3	1	1	28	1	9
1	5	35	12	6	5	8	426	2	71
1	5	5	9	1	2	8	45	9	45
1	6	7	6	3	0	1	42	2	14
1	3	*	*	*	*	*	*	*	*
1	3	*	*	*	*	*	*	*	*
1	3	*	*	*	*	*	*	*	*
2	3	28	9	4	4	10	252	2	63
2	3	164	20	7	5	27	3272	3	467
2	3	7	4	3	1	2	28	1	9
2	3	46	7	4	9	37	322	2	80
2	3	6	6	2	2	5	36	3	18
2	3	34	17	6	5	12	578	3	96
2	3	25	10	5	6	20	250	2	50
2	3	31	9	6	6	19	279	1	46
2	3	8	4	2	2	7	32	2	16
2	3	24	11	4	5	17	264	3	66
2	3	1	2	2	0	0	2	1	1
2	4	58	15	5	14	35	870	3	174
2	4	19	8	4	1	2	152	2	38
2	5	10	7	3	3	5	70	2	23
2	5	69	15	6	1	17	1035	2	172
2	5	24	10	5	1	6	240	2	48
2	5	20	10	4	4	13	200	2	50
2	6	30	8	4	8	18	240	2	60

NOTATION

GP=*DRUG (Bzd / Placebo)*
R=*Radiation weeks*
A1=*Area of reaction*
A2=*Severity of inflammation*
A3=*Inflammation surface*
A4=*Max. Size of Ulceration*
A5=*Total Area of ulceration*
A6=A1 * A2
A7=A2 / A3
A8=A1 * A2 / A3
TBD=Tissue Breakdown
* =*Missing value*

TABLE 3

The measurement of the amount of SALIVA (S1 & S2) & the type Of Radiation (GLAN) in Drug group (GP)

The negative entries of S1 & S2 indicate increased amounts of Saliva at rest (S1) and Saliva during Estimulation (S2).

GP	S1	S2	GLAN
1	-3	-14	1
1	*	*	1
1	-1	-3	1
1	-5	-7	1
1	-2	-3	1
1	*	*	2
1	-2	0	2
1	-4	2	2
1	-2	-1	2
1	3	-1	2
1	-5	1	2
1	-3	-3	2
1	-1	-1	2
1	-1	-5	2
1	-3	0	2
1	-2	-6	2
1	-7	-2	2
1	-4	-2	2
1	*	*	2
1	*	*	2
1	2	-1	3
1	-2	-2	3
1	*	*	3
1	-1	-1	3
1	2	-5	3
2	-3	-4	1
2	-6	-7	1
2	0	-1	1
2	-18	-14	1
2	-9	-11	1
2	-3	-9	1
2	-2	-3	1
2	-3	-2	1
2	*	*	1
2	-1	-1	2
2	3	0	2
2	-3	-3	2
2	-4	-3	2
2	0	-1	2
2	0	1	2
2	1	0	2
2	-8	-4	2
2	-4	-3	3

TABLE 4 *The Tissue Breakdown (A1 to A8), the Saliva produced (S1 & S2) and the Drug group (GP)*

TBD (A1 to A8) was measured BY maximum minus initial valus & SALIVA (S1 & S2) were measured by minimum minus initialvalues A1 to A8 and A1 & S2 are ordered by (S1+S2)

GP	A1	A2	A3	A4	A5	A6	A7	A8	S1	S2
1	7	6	3	0	1	42	2	14	-3	-14
1	13	7	4	3	7	91	2	23	-5	-7
1	6	6	3	1	1	36	2	12	-7	-2
1	6	4	4	1	1	24	1	6	-2	-6
1	8	10	5	1	2	80	2	16	-4	-2
1	40	16	8	2	20	640	2	80	-1	-5
1	10	8	3	2	6	80	3	27	-3	-3
1	3	2	1	1	1	6	2	6	-2	-3
1	17	10	5	1	7	170	2	34	-1	-3
1	25	7	4	1	9	175	2	44	-5	1
1	20	6	3	8	14	120	2	40	-2	-2
1	11	12	3	2	9	132	4	44	-2	-1
1	35	12	6	5	8	426	2	71	2	-5
1	25	10	5	3	8	250	2	50	-3	0
1	8	5	4	1	2	40	1	10	-1	-1
1	13	3	2	1	1	39	1	19	-4	2
1	22	6	3	9	14	132	2	44	-2	0
1	5	9	1	2	8	45	9	45	-1	-1
1	19	11	5	3	12	209	2	42	2	-1
1	22	10	5	1	10	220	2	44	3	-1
1	7	4	3	1	1	28	1	9	*	*
1	*	*	*	*	*	*	*	*	*	*
1	*	*	*	*	*	*	*	*	*	*
1	25	6	3	2	8	153	2	51	*	*
1	*	*	*	*	*	*	*	*	*	*
2	19	8	4	1	2	152	2	38	-18	-14
2	46	7	4	9	37	322	2	80	-9	-11
2	8	4	2	2	7	32	2	16	-6	-7
2	164	20	7	5	27	3272	3	467	-8	-4
2	6	6	2	2	5	36	3	18	-3	-9
2	28	9	4	4	10	252	2	63	-3	-4
2	69	15	6	1	17	1035	2	172	-4	-3
2	10	7	3	3	5	70	2	23	-4	-3
2	58	15	5	14	35	870	3	174	-3	-3
2	20	10	4	4	13	200	2	50	-3	-2
2	25	10	5	6	20	250	2	50	-2	-3
2	24	11	4	5	17	264	3	66	-1	-1
2	24	10	5	1	6	240	2	48	0	-1
2	1	2	2	0	0	2	1	1	0	-1
2	30	8	4	8	18	240	2	60	0	1
2	7	4	3	1	2	28	1	9	1	0
2	31	9	6	6	19	279	1	46	3	0
2	34	17	6	5	12	578	3	96	*	*

NOTE

for notation
see table-2

TABLE 5

The number of weeks of radiation therapy for the two groups: Bzd and Placebo group

GROUP	3 weeks	5 weeks *
Bzd	14	11
Placebo	11	7

* Column heading refer to approximate duration of radiation therapy.

TABLE-6

6.1. *Summary data for Bzd & Placebo groups:*

Time collapse Study variables

GP	V1	V2	V3	V4	V5	V6	V7	V8	A1	A2	A3	A4	A5	S1	S2	NOTATION
1	8	8	7	7	4	4	5	5	35	12	6	5	8	2	-5	GP=DRUG
1	0	0	3	3	0	3	1	0	25	6	3	2	8	*	*	V1=BURNING
1	7	8	6	8	9	9	5	5	5	9	1	2	8	-1	-1	AT REST
1	0	3	0	3	5	5	0	3	*	*	*	*	*	*	*	V2=BURN WITH
1	0	4	0	5	2	4	5	2	19	11	5	3	12	2	-1	EATING
1	6	5	6	6	0	2	2	2	20	6	3	8	14	-2	-2	V3=PAIN AT
1	2	0	0	0	0	5	0	3	13	3	2	1	1	-4	2	REST
1	5	5	5	5	2	5	2	5	8	10	5	1	2	-4	-2	V4=PAIN WITH
1	1	1	0	0	2	3	5	4	11	12	3	2	9	-2	-1	EATING
1	0	1	0	0	2	2	2	3	3	2	1	1	1	-2	-3	V5=BURN WITH
1	3	5	0	2	2	2	3	2	17	10	5	1	7	-1	-3	DRUG
1	8	10	5	7	5	3	2	4	10	8	3	2	6	-3	-3	V6=TASTE OF
1	6	7	3	0	3	4	3	4	8	5	4	1	2	-1	-1	DRUG
1	2	2	1	0	5	0	1	1	40	16	8	2	20	-1	-5	V7=ANALGESIA
1	8	7	0	0	10	7	8	8	25	10	5	3	8	-3	0	DRUG
1	0	0	0	0	0	3	2	2	6	4	4	1	1	-2	-6	V8=TOTAL
1	0	5	0	0	2	0	0	2	6	6	3	1	1	-7	-2	DRUG PAIN
1	4	4	2	5	2	1	3	1	7	6	3	0	1	-3	-14	A1=AREA OF
1	5	8	1	8	0	0	1	1	7	4	3	1	1	*	*	REACTION
1	0	0	0	0	1	2	3	3	*	*	*	*	*	*	*	A2=SEVERITY
1	2	2	0	5	5	2	2	2	22	10	5	1	10	3	-1	OF INFLMN
1	4	2	5	5	5	3	0	4	*	*	*	*	*	*	*	A3=INFLNN
1	8	6	5	6	10	3	2	1	13	7	4	3	7	-5	-7	DURFACE
1	10	10	10	10	10	2	2	10	25	7	4	1	9	-5	1	A4=MAXIMUM
1	1	4	1	1	2	3	2	2	22	6	3	9	14	-2	0	SIZE OF
2	4	1	5	4	0	0	0	0	28	9	4	4	10	-3	-4	ULCERATION
2	4	6	4	5	5	3	5	5	164	20	7	5	27	-8	-4	A5=TOTAL
2	5	0	3	7	5	5	5	5	7	4	3	1	2	1	0	AREA OF
2	4	8	8	9	3	0	2	3	19	8	4	1	2	-18	-14	ULCERATION
2	2	5	2	5	2	5	5	5	24	10	5	1	6	0	-1	S1=SALIVA AT
2	1	5	0	2	1	4	3	2	10	7	3	3	5	-4	-3	REST
2	4	1	7	6	7	2	4	3	25	10	5	6	20	-2	-3	S2=SALIVA
2	8	9	8	8	2	7	4	6	20	10	4	4	13	-3	-2	DURING
2	7	7	0	0	0	3	0	7	31	9	6	6	19	3	0	STIMULATION
2	5	9	0	0	10	2	1	2	24	11	4	5	17	-1	-1	* =MISSING
2	5	7	6	6	10	4	0	9	34	17	6	5	12	*	*	VAULE
2	9	9	8	9	10	1	0	1	58	15	5	14	35	-3	-3	TBD=TISSUE
2	1	1	0	0	0	1	2	1	6	6	2	2	5	-3	-9	BREAKDOWN
2	0	0	0	1	2	2	0	4	46	7	4	9	37	-9	-11	
2	4	2	5	5	5	3	0	4	69	15	6	1	17	-4	-3	
2	9	9	8	9	10	2	0	2	1	2	2	0	0	0	-1	
2	7	8	7	8	2	1	1	1	8	4	2	2	7	-6	-7	
2	0	0	0	5	1	2	1	2	30	8	4	8	18	0	1	

TABLE 6

6.2 Summary data for Bzd & Placebo group:

Background Variables

GP	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	66	1	1	1	0	2	6000	5	109	8	0	0	1	0
1	41	2	1	4	0	1	4688	3	105	3	0	1	1	1
1	71	2	1	2	1	2	6000	5	109	7	0	0	0	1
1	53	1	1	2	1	2	5000	3	109	1	0	0	1	0
1	60	1	1	3	3	2	5000	3	109	3	0	0	1	0
1	67	1	1	1	1	7	5500	3	121	6	1	0	1	0
1	63	1	1	4	1	7	5000	4	93	2	0	0	1	0
1	64	1	1	4	0	3	5000	4	93	6	1	1	1	0
1	63	1	1	3	1	2	5250	3	117	2	0	0	1	0
1	67	2	1	2	0	3	6000	5	109	7	0	0	1	0
1	54	1	1	2	0	5	6000	5	109	4	0	0	0	1
1	73	2	1	3	0	3	5250	3	113	2	1	1	1	0
1	72	2	1	2	0	2	5760	5	102	5	1	0	1	0
1	50	1	1	4	0	3	5250	3	117	3	1	1	0	0
1	76	1	1	3	1	1	5250	3	117	5	1	1	1	0
1	80	2	1	4	0	7	3000	2	70	2	1	1	0	0
1	68	2	5	*	*	8	5000	3	109	5	0	0	0	0
1	61	2	4	4	0	4	6250	6	105	7	0	0	0	0
1	53	1	1	3	0	3	6000	5	138	2	0	0	1	0
1	47	2	3	*	*	8	5000	3	112	4	1	0	0	0
1	78	1	1	2	0	5	6000	5	128	4	0	0	0	0
1	52	1	1	2	1	3	5250	3	133	7	1	0	0	0
1	39	2	4	2	0	7	5250	3	133	7	1	1	1	0
1	58	1	1	4	0	2	6000	5	109	2	0	0	1	0
1	74	2	1	2	0	7	5250	3	109	5	0	0	0	0
2	60	1	1	4	3	1	5000	3	109	3	1	1	0	0
2	55	1	3	*	*	8	5000	3	115	3	0	0	1	0
2	37	2	4	*	*	8	5000	3	105	5	0	0	1	0
2	48	1	4	*	*	4	4500	4	79	4	0	1	1	0
2	46	1	4	*	*	2	6000	5	109	7	1	1	1	0
2	62	1	1	2	1	3	6000	5	109	8	0	0	0	0
2	60	2	1	1	0	1	5250	3	113	8	1	0	1	0
2	36	2	4	2	2	1	6000	5	109	6	0	0	0	1
2	61	1	1	3	1	1	5250	3	113	4	0	0	0	0
2	44	2	1	2	0	1	5250	3	117	3	1	1	0	0
2	61	2	1	3	1	3	5000	3	105	3	0	0	1	0
2	65	2	1	3	0	2	6000	4	120	3	1	1	1	0
2	26	1	1	4	3	3	5000	3	120	2	1	1	0	0
2	56	1	4	3	1	3	5250	3	130	2	0	0	1	0
2	67	1	1	2	1	3	6000	5	123	7	0	0	0	0
2	76	2	1	3	1	3	5000	3	110	3	0	0	1	0
2	44	2	4	*	*	5	4000	3	78	3	0	0	0	1
2	63	2	1	2	0	6	6240	6	*	4	0	0	0	0

NOTATION

GP=DRUG group
A=Age
B=Sex
C=Diagnosis
D=Tumor stage
E=Tumor size
F=Tumor Location
G=Dose
H=Radiation week
I=TDF
J=Last week asses
K=Non-narcotic
L=Narcotic
M=Xylocotic
N=Mucosal infect
*=Missing value

TABLE 7 *The mean and SE of each measurements of: PAIN, SALIVA & Tissue Breakdown (TBD), variables*

	GROUP	
VARIABLE NAME	Bzd	Placebo
PAIN	Mean ± SE	Mean ± SE
Burning at rest	3.60 ± 0.66	4.39 ± 0.67
Burning with eating	4.28 ± 0.63	4.83 ± 0.85
Pain at rest	2.40 ± 0.58	3.94 ± 0.79
Pain with eating	3.44 ± 0.65	4.94 ± 0.75
Burn with drug	3.52 ± 0.65	4.17 ± 0.88
Taste of drug	3.08 ± 0.42	2.61 ± 0.44
Analgesia drug	2.44 ± 0.39	1.83 ± 0.47
Over-all drug pain	3.16 ± 0.45	3.44 ± 0.56

	GROUP	
VARIABLE NAME	Bzd	Placebo
SALIVA	Mean ± SE	Mean ± SE
Saliva level while resting	-2.00 ± 0.60	-3.60 ± 1.17
Saliva level during stimulation	-2.84 ± 0.83	-3.82 ± 0.99

	GROUP	
VARIABLE NAME	Bzd	Placebo
TBD	Mean ± SE	Mean ± SE
Area of reaction	15.36 ± 2.22	33.53 ± 8.74
Severity of inflammation	7.66 ± 0.76	9.56 ± 1.11
Total inflammation surface involved	3.90 ± 0.33	4.22 ± 0.35
Maximum size of ulceration	2.20 ± 0.53	4.26 ± 0.35
Total area of ulceration	6.74 ± 1.19	14.03 ± 2.57
Area of reaction x severity of inflammation	142.14 ± 33.12	451.22 ± 176
Severity of inflammation per surface involved	2.27 ± 0.35	2.11 ± 0.16
Area of reaction x severity of inflammation per surface involved	28.29 ± 4.19	74.78 ± 23.67

TABLE 8.1

THE MEASUREMENT OF PAIN FOR THE TWO GROUPS

	BURN AT REST							*BURN WITH EATING*						
	TIME(weeks)							TIME(weeks)						
GP	0	1	2	3	4	5		GP	0	1	2	3	4	5
1	5	5	5	5	*	*		1	5	5	5	5	*	*
1	0	0	0	5	0	7		1	0	0	0	6	7	8
1	0	0	*	*	*	*		1	0	3	*	*	*	*
1	0	0	0	0	*	*		1	1	0	5	5	*	*
1	0	0	6	0	*	*		1	0	0	0	0	*	*
1	0	2	*	*	*	*		1	0	0	*	*	*	*
1	0	0	4	5	5	*		1	0	0	0	5	5	*
1	7	7	8	*	*	*		1	7	8	8	*	*	*
1	3	0	0	0	0	0		1	3	0	0	4	0	0
1	0	0	3	0	0	*		1	0	5	3	0	0	*
1	0	5	8	*	*	*		1	0	5	10	*	*	*
1	0	0	3	6	6	4		1	0	0	0	7	7	0
1	3	3	4	5	*	*		1	3	3	4	5	*	*
1	2	6	8	10	*	*		1	3	7	10	10	*	*
1	0	0	0	*	*	*		1	0	0	0	*	*	*
1	0	0	0	0	*	*		1	0	0	5	4	*	*
1	2	2	2	2	2	4		1	2	2	2	3	3	6
1	2	0	7	*	*	*		1	0	0	8	*	*	*
1	0	0	0	*	*	*		1	0	0	0	*	*	*
1	1	1	3	1	1	*		1	1	1	0	3	3	*
1	2	2	2	4	*	*		1	3	3	3	5	*	*
1	2	4	8	10	*	*		1	4	5	10	10	*	*
1	0	0	10	*	*	*		1	0	2	10	*	*	*
1	2	0	3	1	*	*		1	4	5	8	5	*	*
2	1	1	5	3	*	*		2	3	2	4	3	*	*
2	0	0	3	4	*	*		2	0	0	3	6	*	*
2	2	2	0	7	*	*		2	0	0	0	0	*	*
2	0	0	0	4	4	*		2	0	0	3	8	8	*
2	0	0	0	2	0	2		2	0	0	0	4	0	5
2	2	0	3	0	0	0		2	0	0	4	4	5	5
2	4	4	6	8	*	*		2	4	4	5	5	*	*
2	0	0	4	6	8	0		2	0	9	8	9	9	0
2	0	0	7	0	*	*		2	0	0	7	0	*	*
2	0	0	2	5	*	*		2	0	0	6	9	*	*
2	3	3	3	8	*	*		2	2	2	8	9	*	*
2	0	0	5	9	*	*		2	1	2	7	10	*	*
2	0	0	1	*	*	*		2	0	0	1	*	*	*
2	4	4	3	*	*	*		2	7	5	4	*	*	*
2	2	2	2	4	6	6		2	3	3	3	5	4	4
2	0	0	5	9	*	*		2	1	2	7	10	*	*
2	0	7	3	1	*	*		2	0	8	6	0	*	*
2	3	3	1	0	0	*		2	2	2	1	0	0	*

TABLE 8.2

THE MEASUREMENT OF PAIN FOR THE TWO GROUPS

PAIN AT REST							*PAIN WITH EATING*						
	TIME(weeks)							TIME(weeks)					
GP	0	1	2	3	4	5	GP	0	1	2	3	4	5
1	0	0	3	7	7	4	1	2	2	4	8	9	8
1	0	0	3	3	*	*	1	0	0	3	3	*	*
1	0	0	0	4	0	6	1	0	0	0	4	5	8
1	0	0	*	*	*	*	1	0	3	*	*	*	*
1	0	0	0	0	*	*	1	0	0	5	5	*	*
1	0	0	6	0	*	*	1	0	0	6	0	*	*
1	0	0	*	*	*	*	1	0	0	*	*	*	*
1	0	0	1	5	5	*	1	0	0	0	5	5	*
1	7	6	7	*	*	*	1	8	8	8	*	*	*
1	0	0	0	0	0	0	1	3	3	0	0	0	0
1	0	0	0	0	0	*	1	0	0	1	2	0	*
1	0	0	5	*	*	*	1	0	0	7	*	*	*
1	0	0	0	0	3	0	1	0	0	0	0	0	0
1	4	4	4	5	*	*	1	5	5	5	5	*	*
1	4	4	4	4	*	*	1	5	5	5	5	*	*
1	0	0	0	*	*	*	1	0	0	0	*	*	*
1	0	0	0	0	*	*	1	0	0	0	0	*	*
1	0	0	0	0	0	0	1	0	0	0	0	0	5
1	5	0	6	*	*	*	1	0	0	8	*	*	*
1	0	0	0	*	*	*	1	0	0	0	*	*	*
1	0	0	0	0	0	*	1	0	0	5	0	0	*
1	0	0	0	0	*	*	1	0	0	0	0	*	*
1	2	4	5	7	*	*	1	4	4	8	10	*	*
1	0	0	10	*	*	*	1	0	0	10	*	*	*
1	0	0	0	0	*	*	1	3	4	4	1	*	*
2	0	1	5	2	*	*	2	1	2	5	3	*	*
2	0	0	3	4	*	*	2	0	0	3	5	*	*
2	2	2	2	5	*	*	2	0	0	0	7	*	*
2	0	0	0	8	5	*	2	0	0	3	9	5	*
2	0	0	0	2	0	2	2	0	0	3	5	0	5
2	0	0	0	0	0	0	2	0	0	0	0	2	2
2	0	0	7	7	*	*	2	0	0	0	6	*	*
2	0	0	2	4	8	0	2	0	3	6	7	8	0
2	0	0	0	0	*	*	2	0	0	0	0	*	*
2	0	0	0	0	*	*	2	0	0	0	0	*	*
2	2	2	6	8	*	*	2	3	3	6	9	*	*
2	0	0	0	8	*	*	2	0	0	0	9	*	*
2	0	0	0	*	*	*	2	0	0	0	*	*	*
2	0	0	0	*	*	*	2	1	2	1	*	*	*
2	0	0	0	0	5	5	2	0	0	0	0	5	5
2	0	0	0	8	*	*	2	0	0	0	9	*	*
2	0	7	2	1	*	*	2	0	8	4	1	*	*
2	0	0	0	0	0	*	2	0	0	5	5	2	*

TABLE 8.3

THE MEASUREMENT OF PAIN FOR THE TWO GROUPS

	BURN WITH DRUG							*TASTE OF DRUG*						
	TIME(weeks)							TIME(weeks)						
GP	0	1	2	3	4	5		GP	0	1	2	3	4	5
1	*	0	0	0	0	4		1	*	0	0	4	4	4
1	*	0	0	0	*	*		1	*	3	3	3	*	*
1	*	0	2	9	9	9		1	*	5	5	5	9	9
1	*	5	*	*	*	*		1	*	5	*	*	*	*
1	*	0	2	2	*	*		1	*	0	4	3	*	*
1	*	0	0	0	*	*		1	*	2	2	0	*	*
1	*	0	*	*	*	*		1	*	5	*	*	*	*
1	*	0	2	2	1	*		1	*	3	5	3	3	*
1	*	2	2	*	*	*		1	*	3	2	*	*	*
1	*	0	0	2	0	0		1	*	0	0	2	0	0
1	*	2	1	1	1	*		1	*	0	2	2	2	*
1	*	5	5	*	*	*		1	*	3	3	*	*	*
1	*	0	3	3	3	1		1	*	0	4	3	2	1
1	*	1	1	5	*	*		1	*	0	0	0	*	*
1	*	6	10	6	*	*		1	*	7	5	5	*	*
1	*	0	0	*	*	*		1	*	3	3	*	*	*
1	*	2	2	2	*	*		1	*	0	0	0	*	*
1	*	1	1	2	2	2		1	*	0	0	0	1	1
1	*	0	0	*	*	*		1	*	0	0	*	*	*
1	*	1	0	*	*	*		1	*	2	2	*	*	*
1	*	2	2	5	5	*		1	*	2	0	2	2	*
1	*	0	0	5	*	*		1	*	1	1	3	*	*
1	*	2	10	10	*	*		1	*	3	3	2	*	*
1	*	2	10	*	*	*		1	*	2	2	*	*	*
1	*	2	2	0	*	*		1	*	3	3	2	*	*
2	*	0	0	0	*	*		2	*	0	0	0	*	*
2	*	0	1	5	*	*		2	*	0	1	3	*	*
2	*	2	2	5	*	*		2	*	2	2	5	*	*
2	*	0	2	3	3	*		2	*	0	0	0	0	*
2	*	0	0	2	0	2		2	*	5	5	5	0	2
2	*	0	1	1	1	1		2	*	0	0	0	4	4
2	*	5	6	7	*	*		2	*	2	2	2	*	*
2	*	2	1	1	2	0		2	*	7	5	5	5	0
2	*	0	0	0	*	*		2	*	3	2	0	*	*
2	*	0	7	10	*	*		2	*	0	2	2	*	*
2	*	0	7	10	*	*		2	*	0	4	4	*	*
2	*	0	5	10	*	*		2	*	0	1	0	*	*
2	*	0	0	*	*	*		2	*	0	1	*	*	*
2	*	2	2	*	*	*		2	*	2	2	*	*	*
2	*	0	0	5	0	0		2	*	1	1	3	2	2
2	*	2	5	10	*	*		2	*	2	1	0	*	*
2	*	2	2	2	*	*		2	*	1	1	1	*	*
2	*	0	0	1	1	*		2	*	2	2	2	2	*

TABEL 8.4

THE MEASUREMENT OF PAIN FOR THE TWO GROUPS

ANALGESIA DRUG							*TOTAL DRUG PAIN*						
	TIME(weeks)							TIME(weeks)					
GP	0	1	2	3	4	5	GP	0	1	2	3	4	5
1	*	0	0	2	4	5	1	*	0	2	3	5	5
1	*	1	1	1	*	*	1	*	0	0	0	*	*
1	*	0	0	5	5	5	1	*	2	3	5	5	5
1	*	0	*	*	*	*	1	*	3	*	*	*	*
1	*	0	5	5	*	*	1	*	0	2	2	*	*
1	*	0	0	0	*	*	1	*	0	2	0	*	*
1	*	0	*	*	*	*	1	*	3	*	*	*	*
1	*	0	0	2	2	*	1	*	0	5	5	5	*
1	*	4	5	*	*	*	1	*	3	4	*	*	*
1	*	0	0	2	0	0	1	*	3	0	2	0	0
1	*	3	2	2	2	*	1	*	0	2	2	2	*
1	*	2	2	*	*	*	1	*	3	4	*	*	*
1	*	0	0	0	0	3	1	*	0	0	4	4	1
1	*	1	1	1	*	*	1	*	1	1	1	*	*
1	*	8	8	8	*	*	1	*	5	8	8	*	*
1	*	2	2	*	*	*	1	*	1	2	*	*	*
1	*	0	0	0	*	*	1	*	2	2	2	*	*
1	*	0	0	3	3	1	1	*	1	1	1	1	1
1	*	0	1	*	*	*	1	*	0	1	*	*	*
1	*	3	0	*	*	*	1	*	3	3	*	*	*
1	*	0	2	0	0	*	1	*	2	1	2	2	*
1	*	0	0	0	*	*	1	*	1	1	4	*	*
1	*	1	1	0	*	*	1	*	1	1	0	*	*
1	*	2	2	*	*	*	1	*	2	10	*	*	*
1	*	2	2	2	*	*	1	*	2	2	1	*	*
2	*	0	0	0	*	*	2	*	0	0	0	*	*
2	*	0	0	5	*	*	2	*	0	1	5	*	*
2	*	2	2	5	*	*	2	*	2	2	5	*	*
2	*	0	0	0	2	*	2	*	0	3	3	3	*
2	*	5	5	1	0	1	2	*	5	5	2	0	1
2	*	0	1	1	3	3	2	*	2	2	2	2	2
2	*	3	3	4	*	*	2	*	2	3	2	*	*
2	*	3	3	3	0	0	2	*	5	5	5	5	0
2	*	0	0	0	*	*	2	*	0	7	0	*	*
2	*	0	1	1	*	*	2	*	0	2	2	*	*
2	*	0	0	0	*	*	2	*	0	7	9	*	*
2	*	0	0	0	*	*	2	*	0	1	0	*	*
2	*	0	2	*	*	*	2	*	0	1	*	*	*
2	*	0	0	*	*	*	2	*	4	3	*	*	*
2	*	0	0	*	0	0	2	*	1	1	4	3	3
2	*	0	0	0	*	*	2	*	2	1	0	*	*
2	*	1	1	1	*	*	2	*	1	1	1	*	*
2	*	0	1	1	1	*	2	*	2	2	2	2	*

TABLE 9.1

THE MEASUREMENT OF TBD FOR THE TWO GROUPS

AREA OF REACTION

TIME (weeks)

GP	0	1	2	3	4	5
1	0	5	30	31	36	27
1	4	2	30	*	*	*
1	25	25	17	19	23	30
1	0	*	*	*	*	*
1	0	1	19	*	*	*
1	1	11	21	8	*	*
1	0	13	*	*	*	*
1	0	0	2	5	8	*
1	0	2	11	*	*	*
1	0	0	*	3	*	*
1	1	6	14	17	18	*
1	0	4	10	*	*	*
1	0	0	6	8	6	*
1	0	2	12	40	*	*
1	0	0	18	25	*	*
1	0	3	6	*	*	*
1	0	0	6	5	*	*
1	1	6	7	6	7	7
1	0	*	7	*	*	*
1	*	*	11	*	*	*
1	0	1	17	20	22	*
1	0	*	*	*	*	*
1	0	2	13	11	*	*
1	0	11	25	*	*	*
1	0	10	22	15	*	*
2	5	8	33	28	*	*
2	4	8	168	98	*	*
2	0	6	4	6	*	*
2	0	6	14	16	19	*
2	0	4	19	24	*	23
2	0	0	8	10	9	10
2	0	4	25	25	*	*
2	0	6	14	14	20	*
2	0	30	31	*	*	*
2	0	0	16	24	*	*
2	0	1	18	34	*	*
2	0	0	20	58	*	*
2	0	0	6	*	*	*
2	3	42	49	*	*	*
2	0	15	45	69	61	*
2	0	1	*	*	*	*
2	0	0	8	7	*	*
2	5	13	23	29	35	*

SEVERITY OF INFLAMMATION

TIME (weeks)

GP	0	1	2	3	4	5
1	0	2	10	12	12	*
1	2	1	*	*	*	*
1	3	3	12	12	12	*
1	0	*	*	*	*	*
1	0	1	*	*	*	*
1	2	3	2	*	*	*
1	0	3	*	*	*	*
1	0	0	5	10	*	*
1	0	1	*	*	*	*
1	0	0	2	*	*	*
1	1	6	11	10	*	*
1	0	3	*	*	*	*
1	0	0	5	2	*	*
1	0	3	16	*	*	*
1	0	0	10	*	*	*
1	0	1	*	*	*	*
1	0	0	6	*	*	*
1	1	2	4	5	5	7
1	0	*	*	*	*	*
1	*	0	*	*	*	*
1	0	1	9	10	*	*
1	0	*	*	*	*	*
1	0	1	7	*	*	*
1	0	5	*	*	*	*
1	0	6	3	*	*	*
2	2	5	10	*	*	*
2	1	3	21	*	*	*
2	0	2	2	*	*	*
2	0	2	8	8	*	*
2	0	1	10	*	9	*
2	0	0	7	6	6	*
2	0	2	6	*	*	*
2	0	4	5	10	*	*
2	0	9	*	*	*	*
2	0	0	11	*	*	*
2	0	1	17	*	*	*
2	0	0	15	*	*	*
2	0	0	*	*	*	*
2	2	8	*	*	*	*
2	0	0	9	15	14	*
2	0	2	*	*	*	*
2	0	0	4	*	*	*
2	1	3	7	9	*	*

TABLE 9.2

THE MEASUREMENT OF TBD FOR THE TWO GROUPS

TOT. INFLAMMATION SURFACE

	TIME (weeks)					
GP	0	1	2	3	4	5
1	0	2	6	6	6	*
1	2	1	*	*	*	*
1	3	3	4	4	4	*
1	0	*	*	*	*	*
1	0	1	*	*	*	*
1	0	2	2	*	*	*
1	0	2	*	*	*	*
1	0	0	3	5	*	*
1	0	1	*	*	*	*
1	0	0	1	*	*	*
1	1	3	6	6	*	*
1	0	2	*	*	*	*
1	0	0	3	2	*	*
1	0	2	8	*	*	*
1	0	0	5	*	*	*
1	0	1	*	*	*	*
1	0	0	3	*	*	*
1	1	2	3	3	3	4
1	0	*	*	*	*	*
1	*	0	*	*	*	*
1	0	1	5	5	*	*
1	0	*	*	*	*	*
1	0	1	4	*	*	*
1	0	4	*	*	*	*
1	0	3	3	*	*	*
2	2	5	5	*	*	*
2	1	3	8	*	*	*
2	0	2	2	*	*	*
2	0	2	4	4	*	*
2	0	2	5	*	5	*
2	0	0	3	3	3	*
2	0	2	3	*	*	*
2	0	3	2	4	*	*
2	0	6	*	*	*	*
2	0	0	4	*	*	*
2	0	1	6	*	*	*
2	0	0	5	*	*	*
2	0	0	*	*	*	*
2	1	5	*	*	*	*
2	0	0	5	6	6	*
2	0	2	*	*	*	*
2	0	0	2	*	*	*
2	1	2	5	5	*	*

MAX. SIZE OF ULCERATION

	TIME (weeks)					
GP	0	1	2	3	4	5
1	0	0	4	4	5	*
1	0	1	*	*	*	*
1	0	0	2	2	1	*
1	0	*	*	*	*	*
1	0	0	*	*	*	*
1	0	8	6	*	*	*
1	0	1	*	*	*	*
1	0	0	1	1	*	*
1	0	0	*	*	*	*
1	0	0	1	*	*	*
1	0	0	1	1	*	*
1	0	0	*	*	*	*
1	0	0	1	1	*	*
1	0	0	2	*	*	*
1	0	0	3	*	*	*
1	0	0	*	*	*	*
1	0	0	0	*	*	*
1	0	0	0	0	0	0
1	0	*	*	*	*	*
1	*	0	*	*	*	*
1	0	0	1	1	*	*
1	0	*	*	*	*	*
1	0	0	3	*	*	*
1	0	0	*	*	*	*
1	0	2	9	*	*	*
2	1	1	5	*	*	*
2	0	0	1	*	*	*
2	0	1	0	*	*	*
2	0	0	1	1	*	*
2	0	0	1	*	1	*
2	0	0	3	1	2	*
2	0	0	6	*	*	*
2	0	1	2	4	*	*
2	0	5	*	*	*	*
2	0	0	5	*	*	*
2	0	0	5	*	*	*
2	0	0	14	*	*	*
2	0	0	*	*	*	*
2	0	9	*	*	*	*
2	0	0	1	1	1	*
2	0	0	*	*	*	*
2	0	0	2	*	*	*
2	0	1	8	6	*	*

TABLE 9.3

THE MEASUREMENT OF TBD FOR THE TWO GROUPS

TOTAL AREA OF ULCERATION

TIME (weeks)

GP	0	1	2	3	4	5
1	0	0	5	5	8	*
1	0	1	*	*	*	*
1	0	0	8	6	8	*
1	0	*	*	*	*	*
1	0	0	*	*	*	*
1	0	9	8	*	*	*
1	0	1	*	*	*	*
1	0	0	2	3	*	*
1	0	0	*	*	*	*
1	0	0	1	*	*	*
1	0	0	3	3	*	*
1	0	0	*	*	*	*
1	0	0	2	2	*	*
1	0	0	20	*	*	*
1	0	0	8	*	*	*
1	0	0	*	*	*	*
1	0	0	0	*	*	*
1	0	0	0	0	0	1
1	0	*	*	*	*	*
1	*	0	*	*	*	*
1	0	0	10	7	*	*
1	0	*	*	*	*	*
1	0	0	7	*	*	*
1	0	1	*	*	*	*
1	0	6	12	*	*	*
2	1	2	11	*	*	*
2	0	0	27	*	*	*
2	0	2	0	*	*	*
2	0	0	2	1	*	*
2	0	0	7	*	3	*
2	0	0	5	2	3	*
2	0	0	20	*	*	*
2	0	2	5	13	*	*
2	0	16	*	*	*	*
2	0	0	17	*	*	*
2	0	0	13	*	*	*
2	0	0	35	*	*	*
2	0	0	*	*	*	*
2	0	26	*	*	*	*
2	0	0	13	17	8	*
2	0	0	*	*	*	*
2	0	0	7	*	*	*
2	0	1	17	18	*	*

TABLE 10

THE MEASUREMENT OF SALIVA FOR THE TWO GROUPS

SLIVA AT REST

	TIME(weeks)					
GP	0	1	2	3	4	5
1	*	0	0	0	*	*
1	1	0	0	1	3	5
1	4	*	*	*	*	*
1	3	6	7	*	*	*
1	5	3	4	6	*	*
1	5	2	*	*	*	*
1	6	5	5	4	3	*
1	3	2	2	*	*	*
1	3	2	*	1	*	*
1	6	7	5	5	6	*
1	4	1	1	*	*	*
1	1	1	1	1	1	*
1	4	3	6	6	*	*
1	3	1	1	1	*	*
1	4	3	2	*	*	*
1	7	2	1	0	*	*
1	3	1	1	2	0	1
1	9	*	*	*	*	*
1	*	1	2	*	*	*
1	2	6	6	9	8	*
1	0	*	*	*	*	*
1	6	5	5	4	*	*
1	6	1	*	*	*	*
1	7	5	6	*	*	*
2	5	4	3	2	*	*
2	9	2	4	1	*	*
2	3	4	3	4	*	*
2	20	5	4	3	2	*
2	1	1	3	3	*	2
2	5	2	2	1	0	*
2	3	2	3	1	*	*
2	4	4	3	3	3	*
2	5	8	9	*	*	*
2	1	1	1	*	*	*
2	*	2	0	1	*	*
2	4	4	2	1	*	*
2	4	1	1	*	*	*
2	13	4	3	*	*	*
2	7	6	5	5	3	5
2	3	3	*	*	*	*
2	9	4	3	3	*	*
2	3	4	4	*	3	*

SALIVA DURING STIMULATION

	TIME(weeks)					
GP	0	1	2	3	4	5
1	*	0	0	0	*	*
1	2	3	1	4	3	4
1	5	*	*	*	*	*
1	3	1	4	*	*	*
1	12	10	11	12	*	*
1	5	8	*	*	*	*
1	5	4	3	3	3	*
1	5	5	4	*	*	*
1	4	3	*	1	*	*
1	9	7	5	6	6	*
1	7	6	3	*	*	*
1	3	4	3	2	3	*
1	7	3	6	7	*	*
1	0	0	0	0	*	*
1	8	3	2	*	*	*
1	2	2	0	1	*	*
1	13	2	1	2	0	0
1	3	*	*	*	*	*
1	*	9	7	*	*	*
1	10	9	9	8	8	*
1	1	*	*	*	*	*
1	9	3	3	3	*	*
1	1	1	*	*	*	*
1	3	3	3	*	*	*
2	6	2	2	2	*	*
2	5	3	3	1	*	*
2	2	5	3	3	*	*
2	17	6	4	4	4	*
2	5	4	6	9	*	9
2	5	4	6	6	1	*
2	4	2	3	2	*	*
2	3	3	4	4	4	*
2	4	5	3	*	*	*
2	4	4	3	*	*	*
2	*	5	1	1	*	*
2	4	4	2	1	*	*
2	9	1	0	*	*	*
2	13	3	2	*	*	*
2	8	6	5	5	6	7
2	4	3	*	*	*	*
2	9	4	2	2	*	*
2	3	4	5	*	4	*

TABLE 11

11.1 The number of missing values for the measurements of PAIN in the two groups

The measurements of PAIN:

Burn at rest, Burn with eating, Pain at rest, & Pain with eating

TIME (weeks)

Group	0	1	2	3	4	5	N
Bzd	0	0	2	8	17	20	25
Placebo	0	0	0	2	12	14	18

Group	0	1	2	3	4	5	N
Bzd	0	0	2	8	17	20	25
Placebo	0	0	0	2	12	14	18

Group	0	1	2	3	4	5	N
Bzd	0	0	2	8	17	20	25
Placebo	0	0	0	2	12	14	18

Group	0	1	2	3	4	5	N
Bzd	0	0	2	8	17	20	25
Placebo	0	0	0	2	12	14	18

11.2 The number of missing values for the measurements of PAIN in the two groups

The measurements of PAIN:

Burn with drug, Taste of drug, Analgesia drug, & Total pain

TIME (weeks)

Group	0	1	2	3	4	5	N
Bzd	-	0	2	8	17	20	25
Placebo	-	0	0	2	12	14	18

Group	0	1	2	3	4	5	N
Bzd	-	0	2	8	17	20	25
Placebo	-	0	0	2	12	14	18

Group	0	1	2	3	4	5	N
Bzd	-	0	2	8	17	20	25
Placebo	-	0	0	3	12	14	18

Group	0	1	2	3	4	5	N
Bzd	-	0	2	8	17	20	25
Placebo	-	0	0	2	12	14	18

11.3 The number of missing values for the measurements of Tissue Breakdown (TBD) in the two groups

The measurements of TBD:

Area of reaction, Severity of inflammation, Total-inflammation surface, Maximum size of ulceration

TIME (weeks)

Group	0	1	2	3	4	5	N
Bzd	1	4	4	11	18	22	25
Placebo	0	0	1	4	13	15	18

Group	0	1	2	3	4	5	N
Bzd	1	3	11	18	22	24	25
Placebo	0	0	4	13	15	18	18

Group	0	1	2	3	4	5	N
Bzd	1	3	11	18	22	24	25
Placebo	0	0	4	13	15	18	18

Group	0	1	2	3	4	5	N
Bzd	1	3	11	18	22	24	25
Placebo	0	0	4	13	15	18	18

11.4 The number of missing values for the measurements of Tissue Breakdown (TBD) in the two groups

The measurements of TBD:

Total area of ulceration

TIME (weeks)

Group	0	1	2	3	4	5	N
Bzd	1	3	11	18	22	24	25
Placebo	0	0	4	13	15	18	18

The number of missing values for the measurements of SALIVA in the two groups

The measurements of SALIVA:

Saliva while at rest, Saliva during stimulation

TIME (weeks)

Group	0	1	2	3	4	5	N
Bzd	2	3	6	11	18	22	25
Placebo	1	0	1	6	13	16	18

Group	0	1	2	3	4	5	N
Bzd	2	3	6	11	18	22	25
Placebo	1	0	1	6	13	16	18

FIGURES

The measurement of Pain;

Fig 1.1(a) The means of the burn at rest for the Bed group

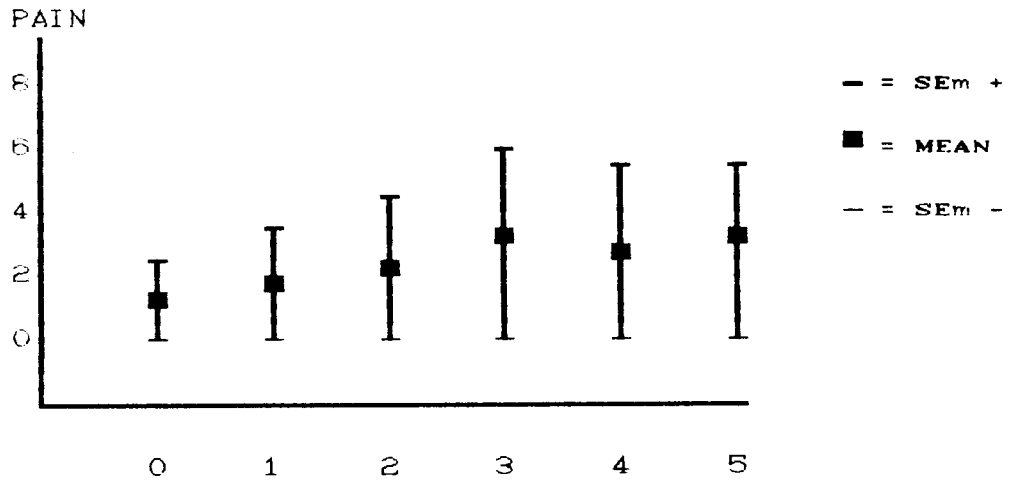


Fig 1.1(b) The means of the burn at rest for the placebo group

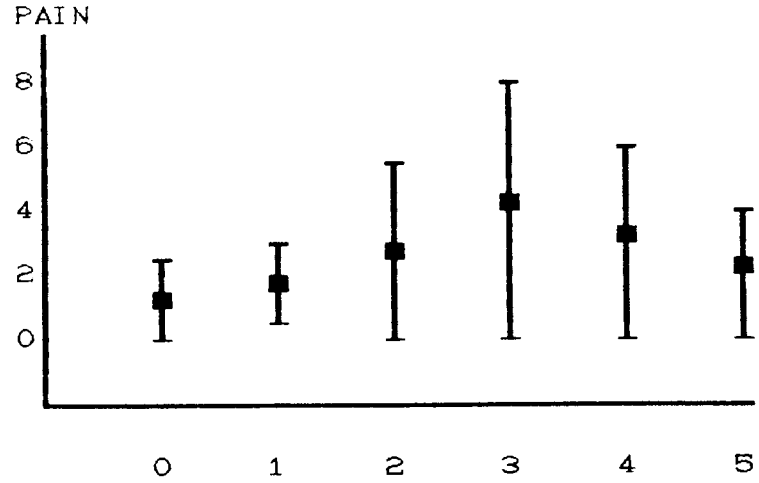


Fig 1.2(a) The means of the burn with eating for the Bzd group

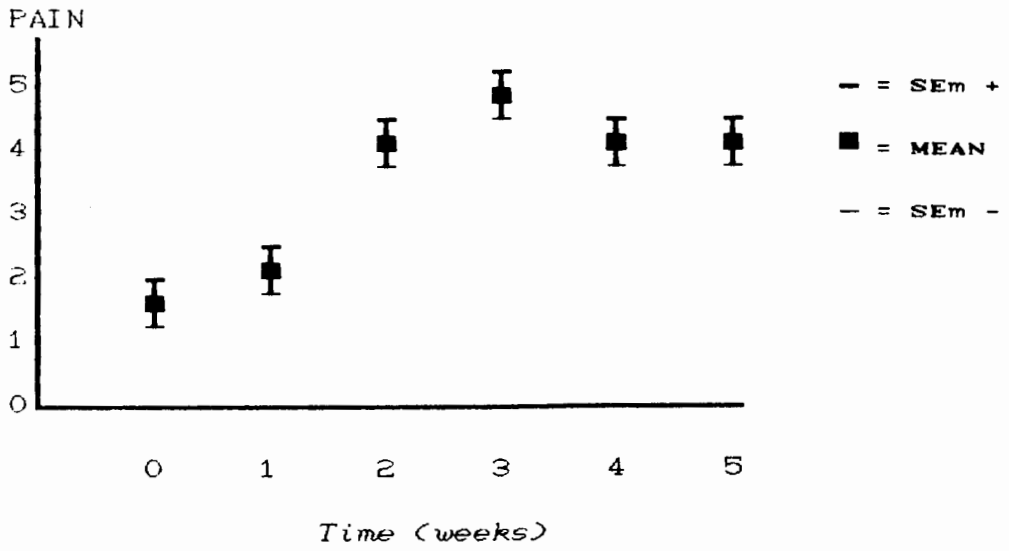


Fig 1.2(b) The means of the burn with eating for the placebo group

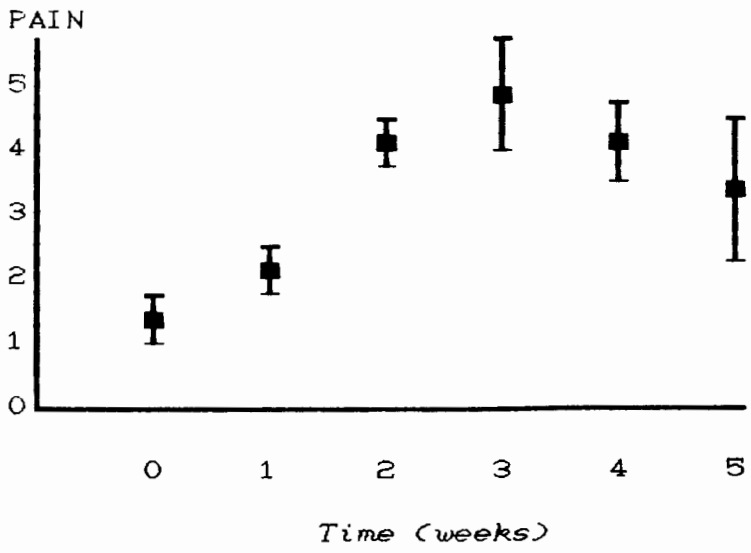


Fig 1.3(a) The means of the Pain at rest for the Bzd group

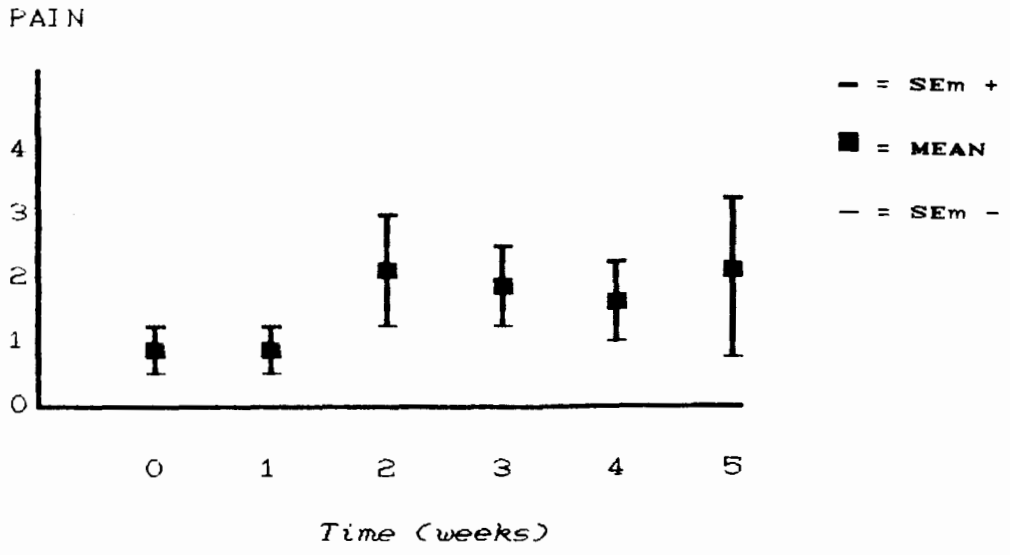


Fig 1.3(b) The means of the Pain at rest for the placebo group

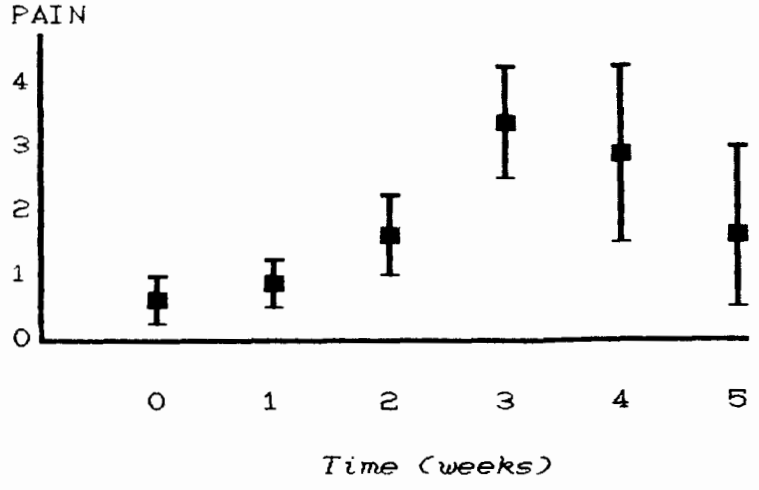


Fig 1.4(a) The means of the Pain with eating for the Bzd group

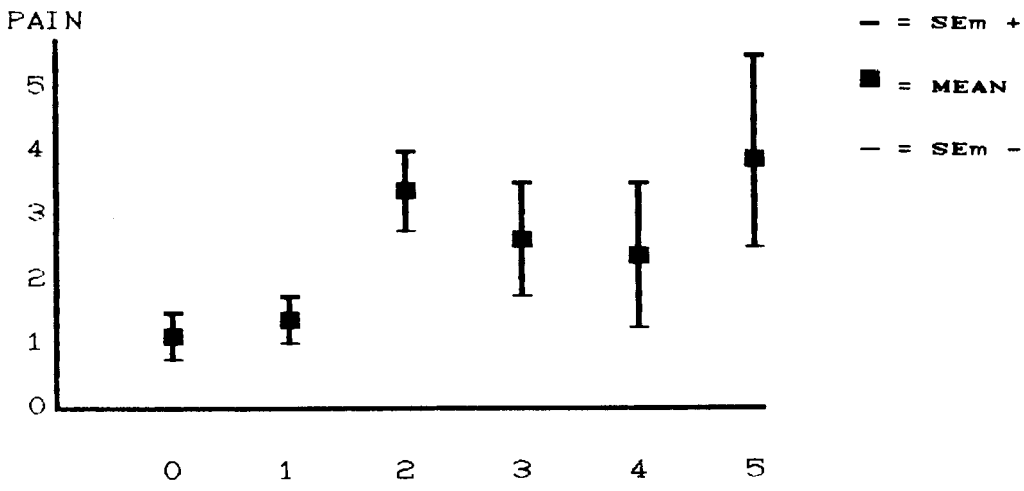


Fig 1.4(b) The means of the Pain with eating for the placebo group

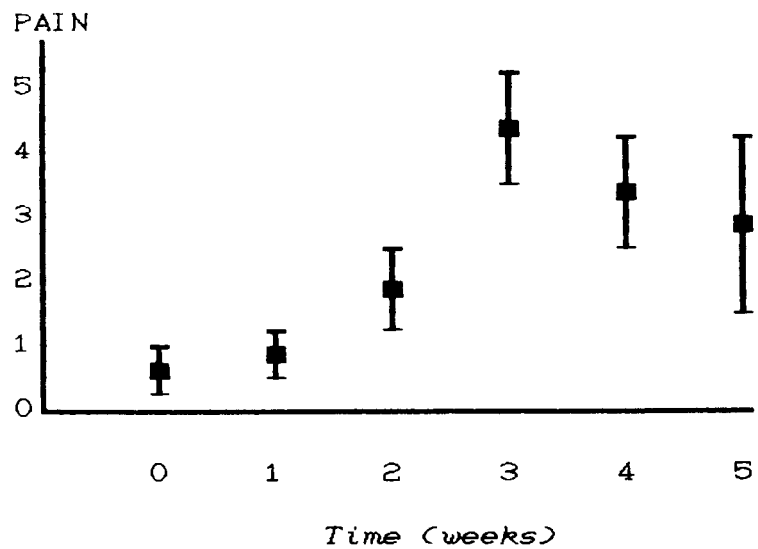


Fig 1.5(a) The means Of the Burn with drug for the Bzd group

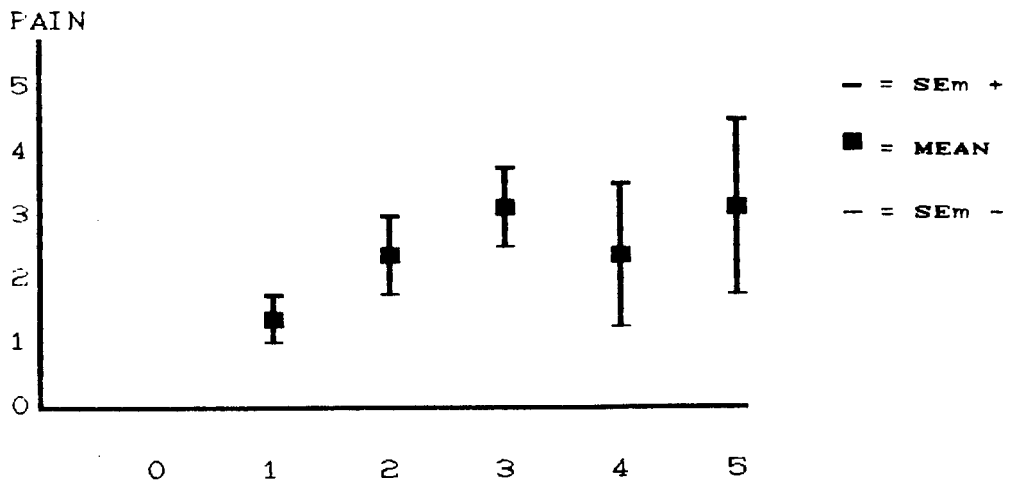


Fig 1.5(b) The means of the Burn with drug for the placebo group

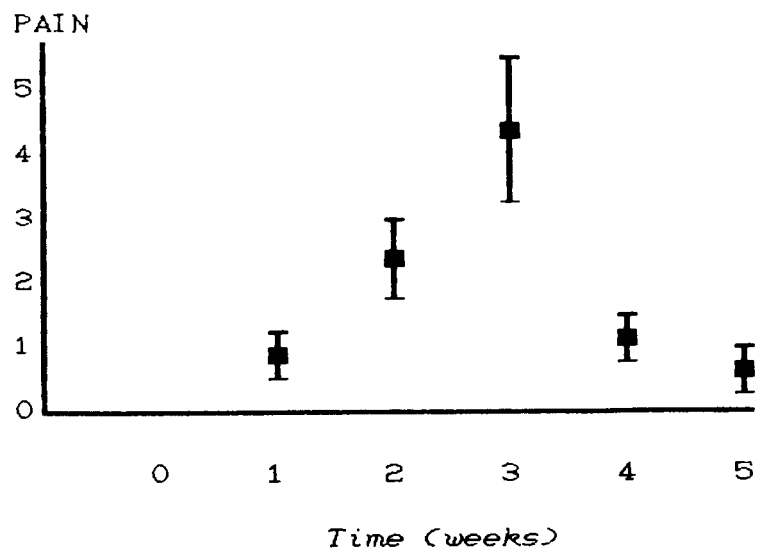


Fig 1.6(a) The means of the Taste of drug for the Bzd group

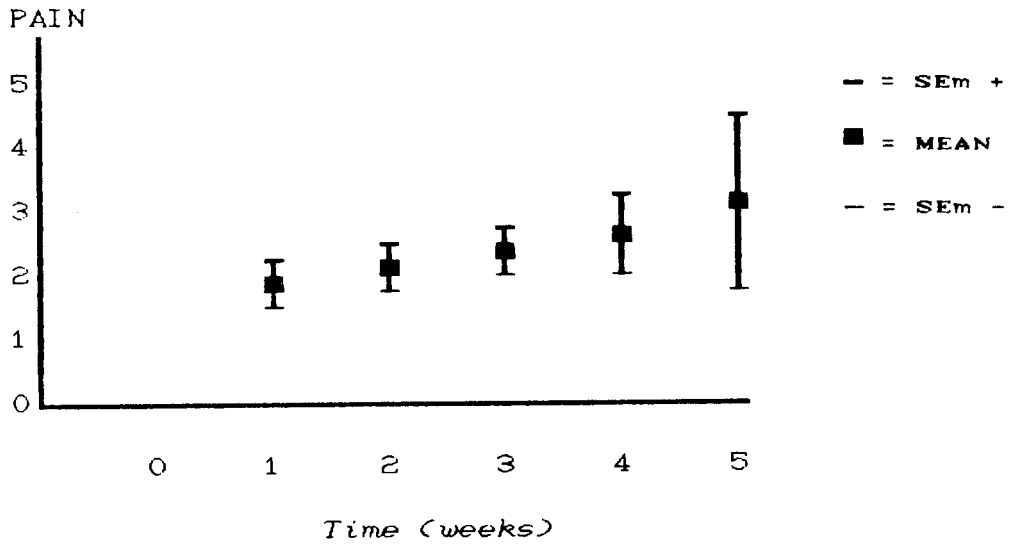


Fig 1.6(b) The means of the Taste of drug for the placebo group

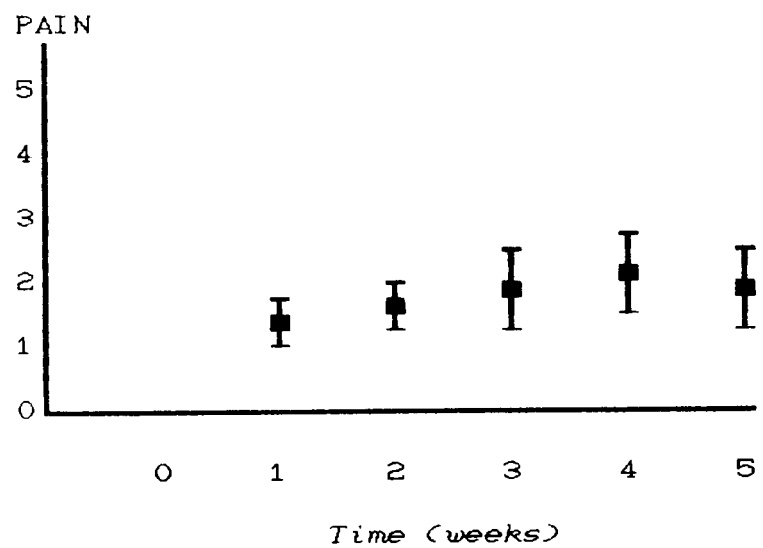


Fig 1.7(a) The means of the Analgesia drug for the Bzd group

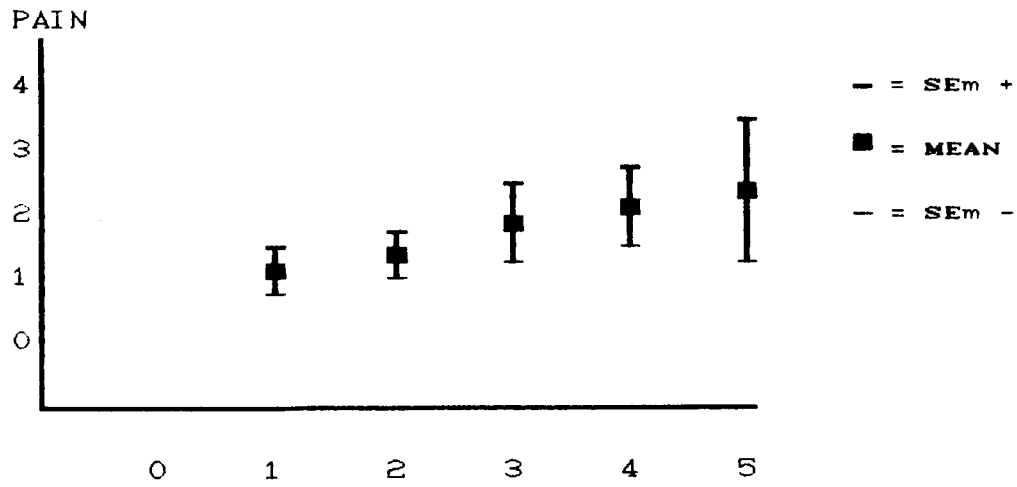


Fig 1.7(b) The means of the Analgesia drug for the placebo group

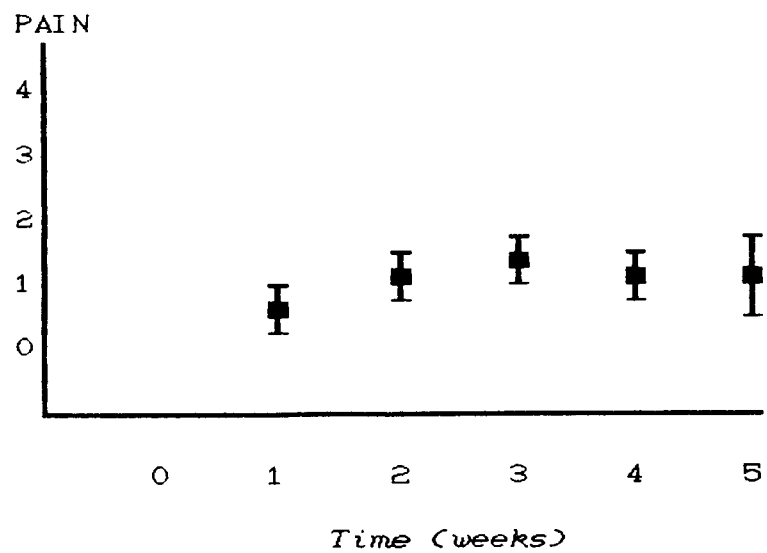


Fig 1.8(a) The means of the Total pain of drug for the Bzd group

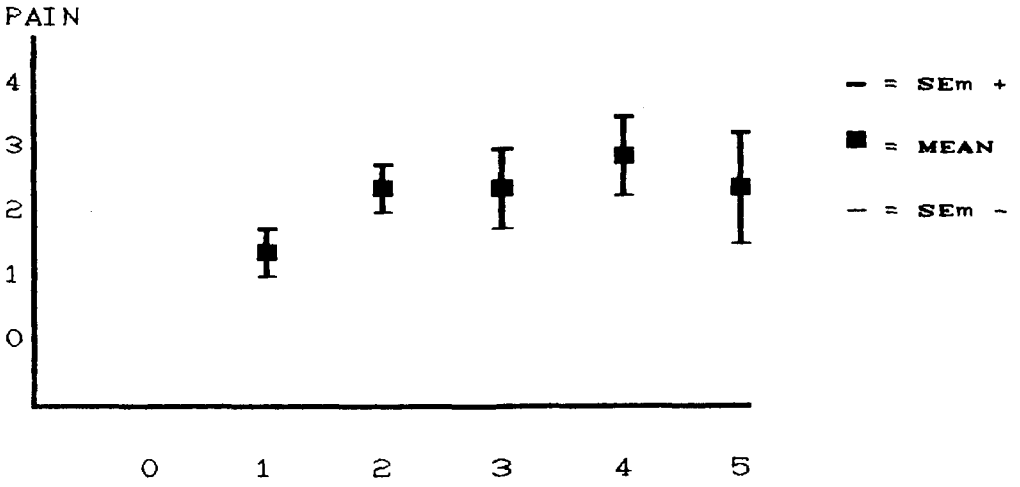
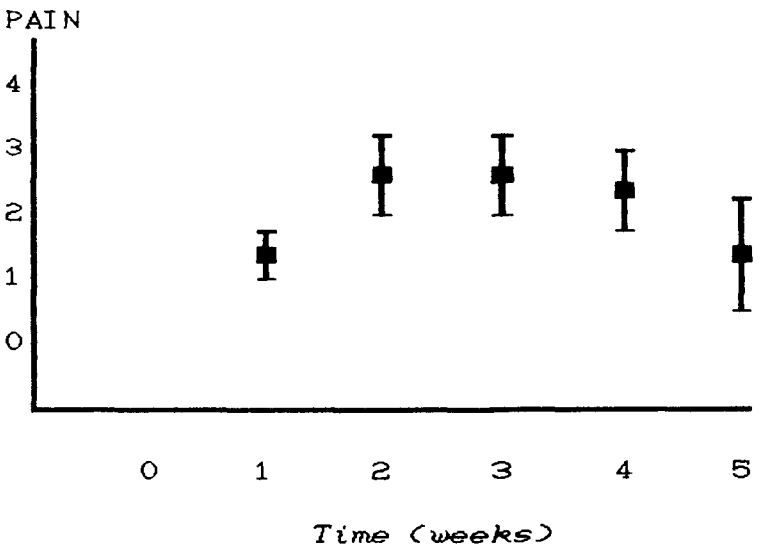


Fig 1.8(b) The means of the Total pain of drug for the placebo group



The Measurement Of Tissue Breakdown (TBD)

Fig 2.1(a) The means of Area of reaction for the Bzd group

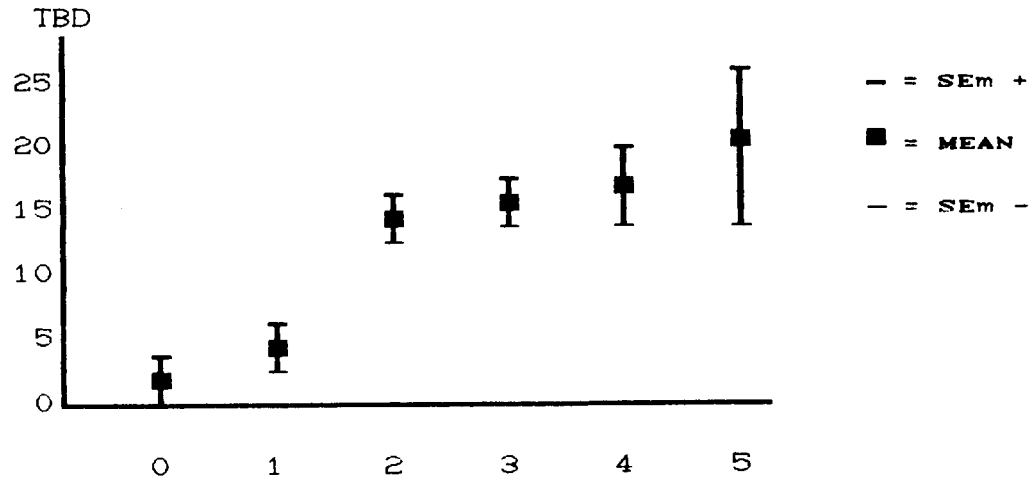
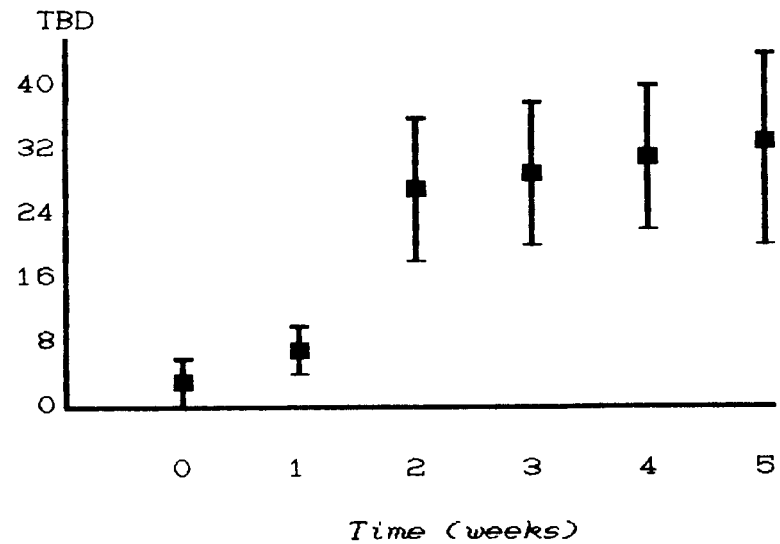


Fig 2.2(b) The means of the Area of reaction for the placebo group



The Measurement Of Tissue breakdown

Fig 2.2(a) The means of Severity of inflammation for the Bzd group

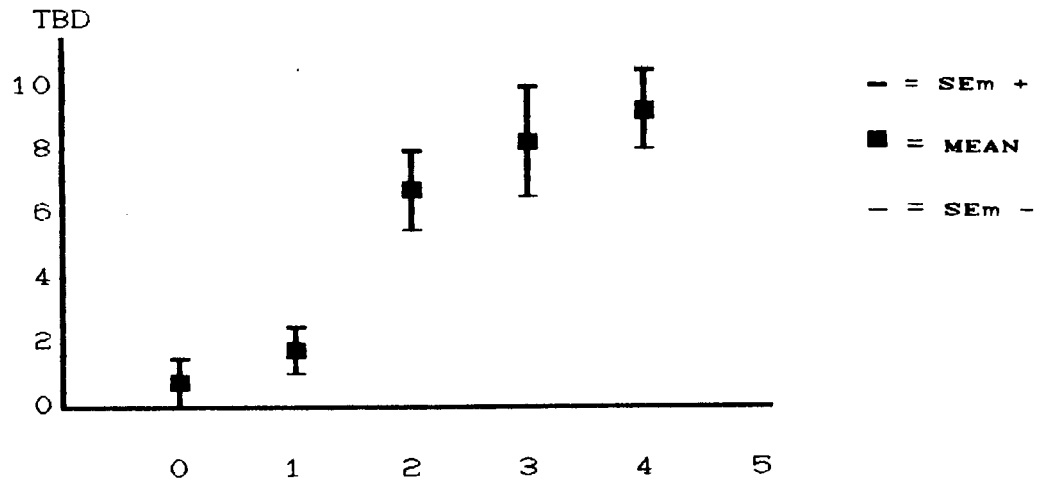


Fig 2.2(b) The means of the Severity of inflammation for the placebo group

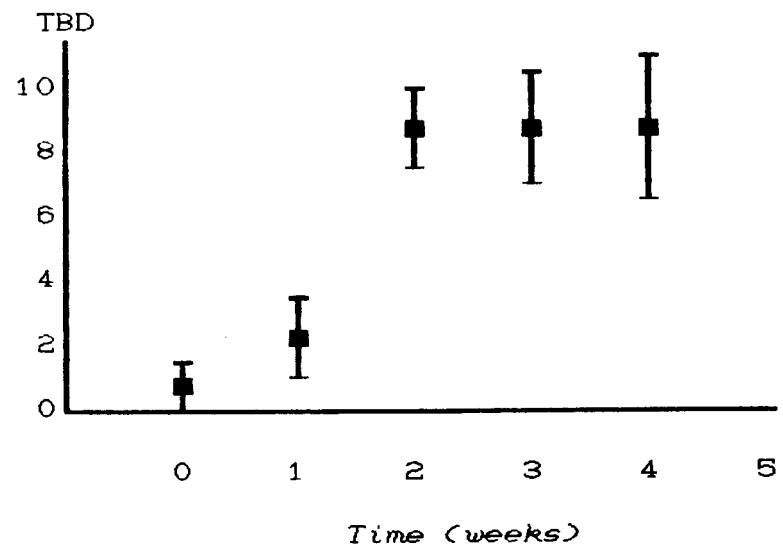


Fig 2.3(a) The means of Total inflammation surface for the Bzd group

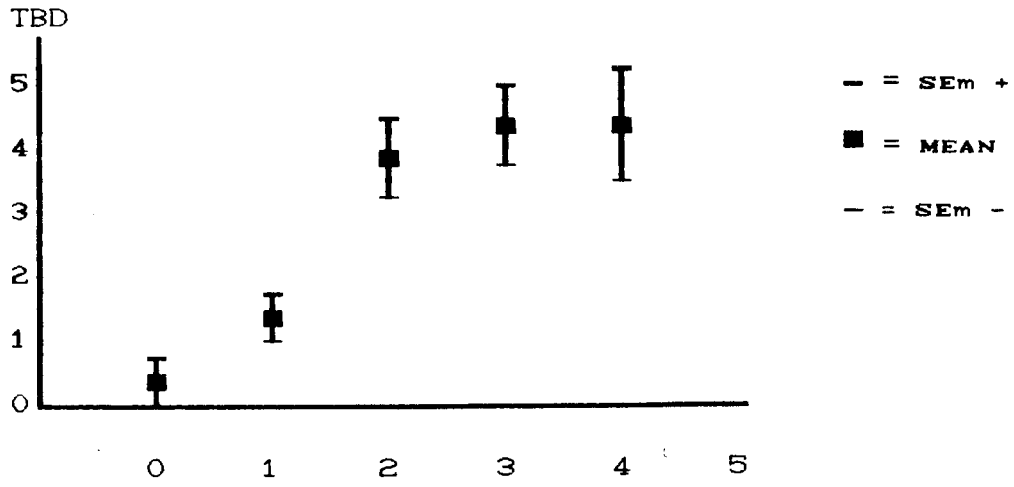


Fig 2.3(b) The means of Tatal inflammation surface for the placebo group

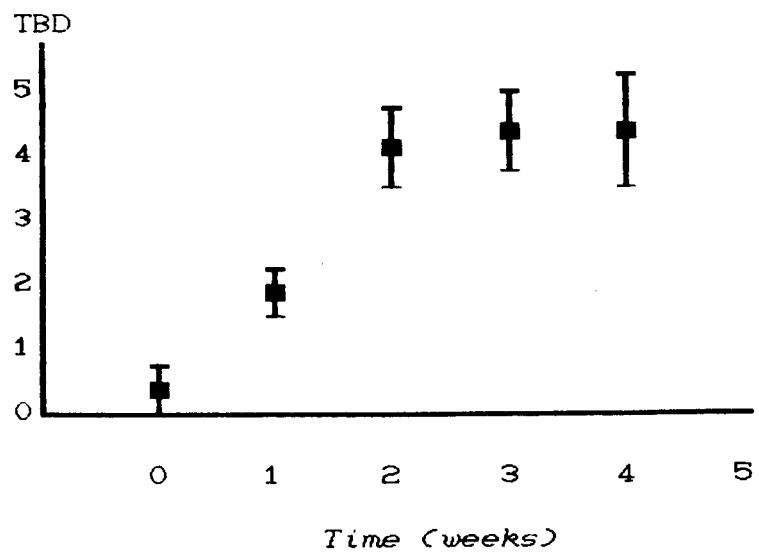


Fig 2.4(a) The means of Maximum size of ulceration for the Bzd group

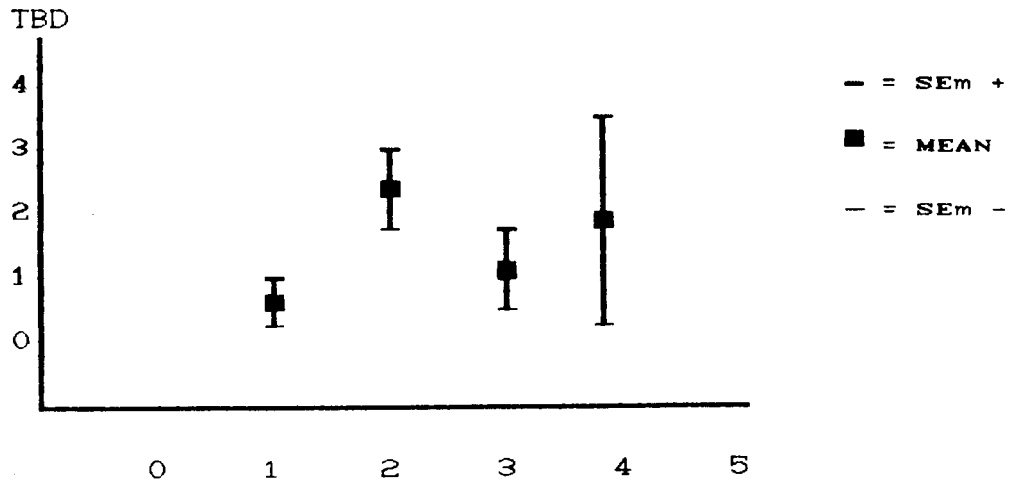


Fig 2.4(b) The means of Maximum size of ulceration for the placebo group

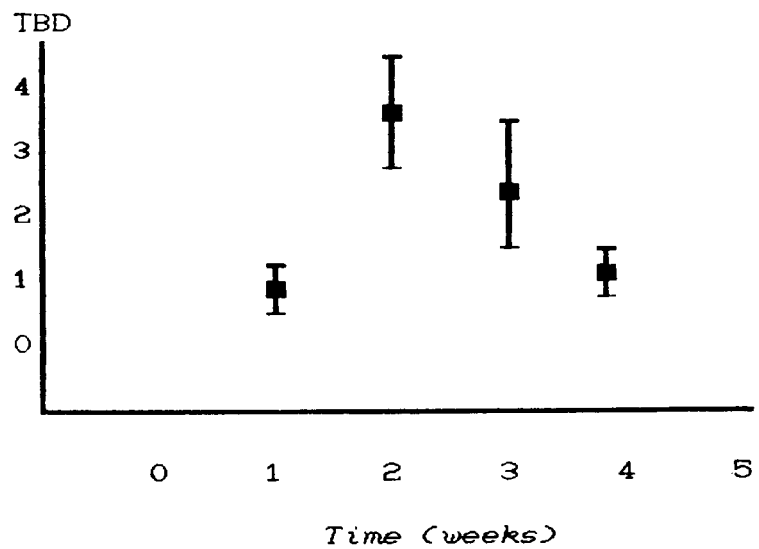


Fig 2.5(a) The means of Total area of ulceration for the Bzd group

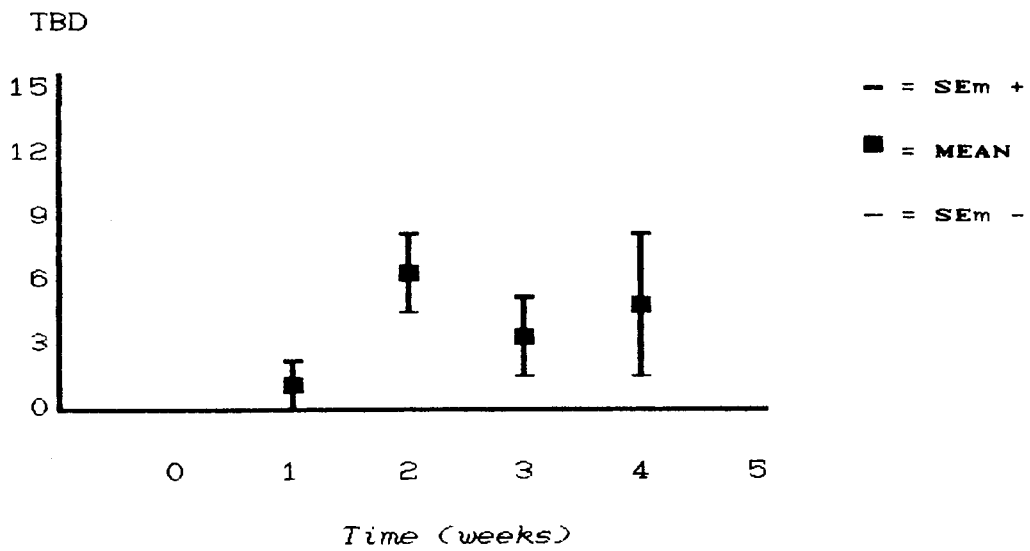


Fig 2.5(b) The means of Total area of ulceration for the placebo group

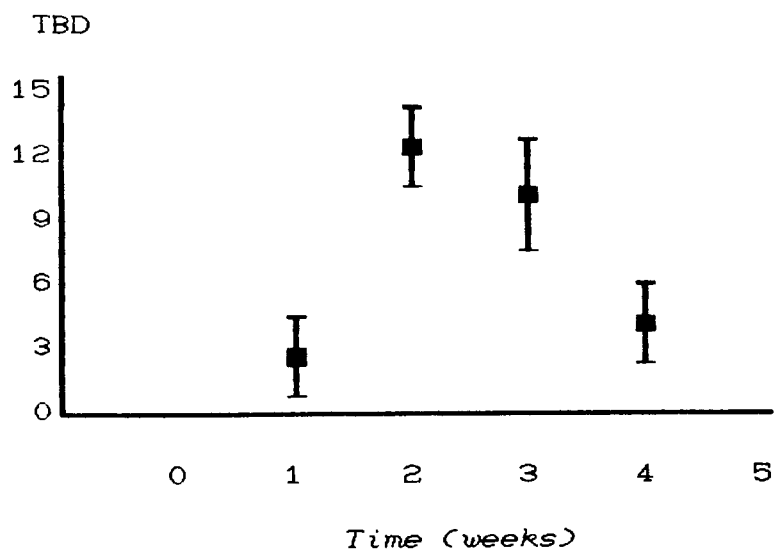


Fig 3.1(a) The means of Saliva while at rest for the Bzd group

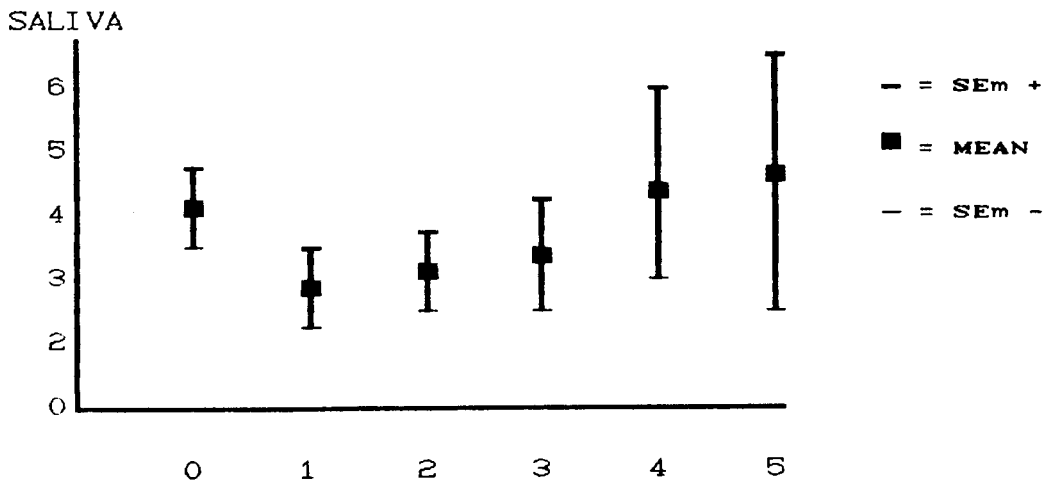


Fig 3.1(b) The means of Saliva while at rest for the placebo group

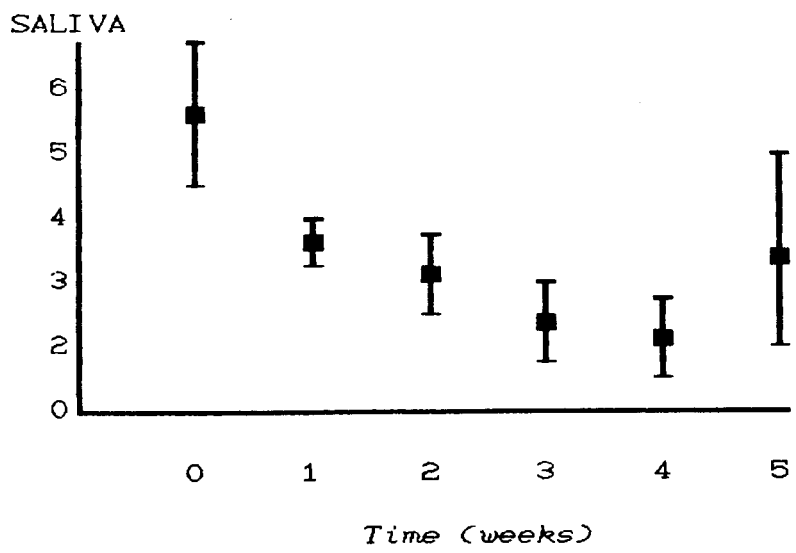


Fig 3.2(a) The means of Saliva during stimulation for the Bzd group

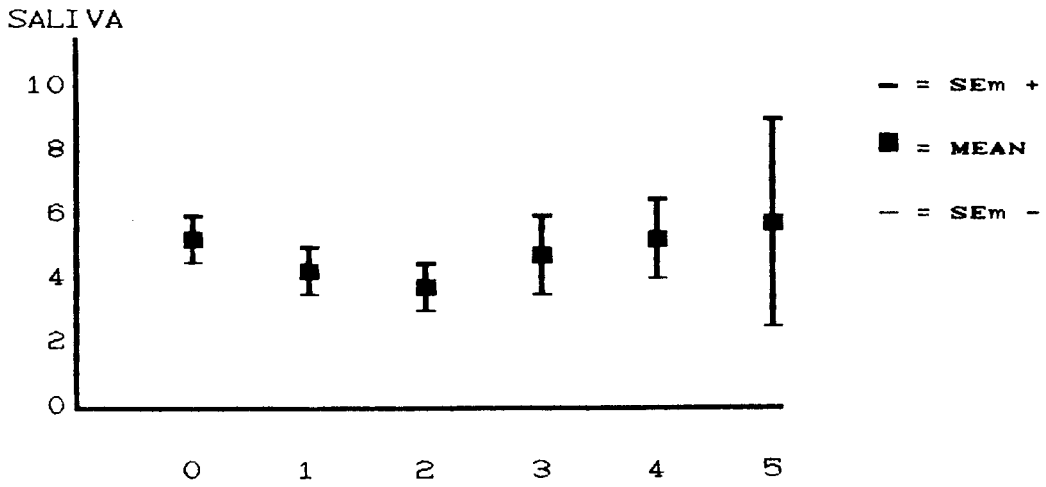
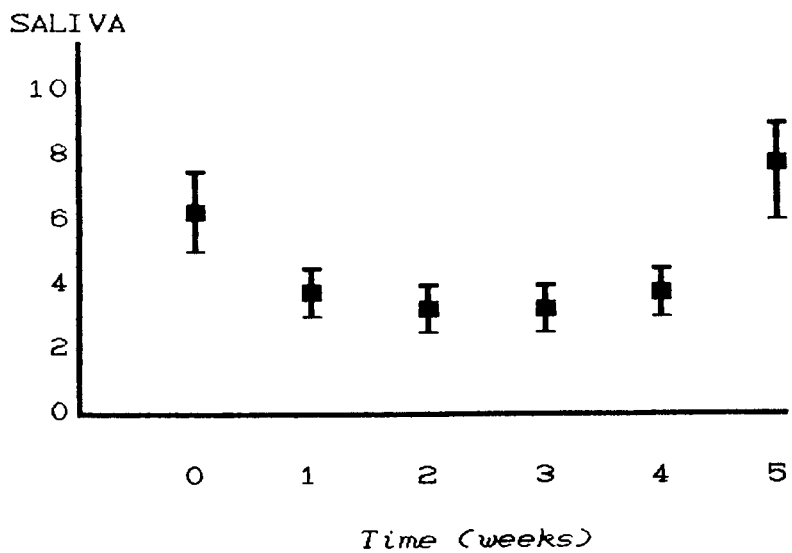


Fig 3.2(b) The means of Saliva during stimulation for the placebo group



APPENDIX-A

- Iteratively Reweighted Least Squares

The purpose of this section is to show how McCullagh attempts to find the MLE for the cumulative logit model. In fact, McCullagh did not show how to find the MLE in GLIM, he just pointed out how to find the estimated values via a quasi-likelihood function (QLHD). This process required a modification of the estimation algorithm of the generalized linear model (GLM) in order to adapt the Gauss-Newton algorithm used by the QLHD.

The QLHD function was proposed by Wedderburn (1972) in fitting the GLM. The statistical properties of the QLHD function are similar to those of the ordinary log-likelihood, except that the dispersion parameter σ^2, when it is unkown, is treated separately from the parameter β and is not estimated by weighted least squares.

McCullagh pointed out that, since the quasi-likelihood (QLHD) function is invariant under invertible linear transformations, there is no difference whether we use the cumulative observation Z_{ij} or the actual observation Y_{ij} in the maximization of the likelihood function.

However, McCullagh shows that if $Z = LY$ where L is the lower triangular matrix, then the expectation and var-cov of the Z should be expressed by $n\gamma = nL\Pi$ and $\sigma^2 LVL^T$ respectively, where $n\Pi$ is the expectation of Y and $\sigma^2 nV$ is var-cov matrix of Y.

Now let the $Y_1, \ldots, Y_m$ be a random sample of multinomial vectors where each $Y_i = (Y_{i1}, \ldots, Y_{ik})$ is a k-nomial distribution with the n_i trial. Let Π_{ij} be the probability of outcome J in the n_i trail. The covariate vector X_i associated with the (i,j) cell of the K-nomial observation usually denoted as: $X_i = (X_{i1}, \ldots, X_{ip})$.

The likelihood of a k-nomial vector is given by

$$L_i = \begin{bmatrix} n_i \\ Y_{i1} \ldots Y_{ik} \end{bmatrix} \Pi_{ik}^{Y_{i1}} \ldots \Pi_{ik}^{Y_{ik}}$$

$$= K_i \cdot \exp[\, Y_{i1} \ln(\Pi_{i1}) + \ldots + Y_{ik} \ln(\Pi_{ik}) \,] \qquad (1)$$

Then the log-likelihood l for m observation Y_{ij} having k categories could be written as:

$$l(\Pi(\beta); Y) = \sum\sum Y_{ij} \log(\Pi_{ij}) \qquad (2)$$

where, $\sum\sum \Pi_{ij} = 1$ and $\Pi(\beta)$ is parameterized into parameter $\beta = (\beta_1, \beta_2, \ldots, \beta_p)$.

Thus the maximum likelihood equation for β can be written as

follows:

Since $\frac{\partial l}{\partial \Pi(\beta)} = V^{-}(Y - n\Pi)$

then $$\frac{\partial l}{\partial \beta} = \frac{\partial l}{\partial \Pi} * \frac{\partial \Pi}{\partial \beta}$$

$$= \left(\frac{\partial \Pi}{\partial \beta}\right)^{T} V^{-}(Y - n\Pi) = 0 \qquad (3)$$

$$= D^{T}V^{-}(Y - n\Pi)$$

$$= D^{T}W(n^{-1}Y - \Pi) = 0 \qquad (4)$$

where, $D = \frac{\partial \Pi}{\partial \beta}$, $W = n^{-1}V^{-}$ and V^{-} is a generalized inverse of V. Since the variance of Y relies on Π which is in turn some function of β, then to solve (4) it is more appropriate to use some iteration scheme which at each iteration uses the preceeding estimate of β to produce an updated (new) estimate of β. The Fisher scoring method was used in these iterative procedures to produce the maximum likelihood estimates of β.

Denote I_{β} to be the Fisher information matrix of the model under discussion and S_{β} is the score function.

$$I_{\beta} = E\left(-\frac{\partial^{2} l}{\partial \beta^{2}}\right)$$

$$= D^{T}V^{-}D \qquad (5)$$

$$S_{\beta} = \frac{\partial\, l}{\partial\, \beta}$$

$$= D^{T}V\,(Y - n\Pi) \qquad (6)$$

To determine the values of β, the log LHD or Q-LHD needs to be maximized in order to calculate the roots of the equation (4). These equations are non-linear in β, so a numerical algorithm is needed to find the roots. Here, the Fisher scoring algorithm is given by:

$$\hat{\beta}_{1} - \hat{\beta}_{o} = I_{\beta}^{-1} S_{\beta}$$

$$= [\ D^{T}V^{-}D\ ]^{-1}[D^{T}V^{-}(Y - n\Pi)\ ]$$

This is readily recognized as the Gauss-Newton algorithm for fitting the response Π to the observations Y with weight W. The maximum likelihood estimation can be carried out via a non-linear regression program, such as BMDP3R, which uses the Gauss-Newton algorithm. This result is intuitively reasonable since, after all we could view $Y = \Pi + \varepsilon$, with $E(\varepsilon) = 0$. Then using $\hat{\beta}_{o}$, as initial values, the updated (new) estimate value is $\hat{\beta}_{1}$, again we use β_{1} as initial value to get the updated estimate value β_{2}, this iterative procedure of estimation is repeated until the sequence of estimation converges. That is, the iteration is terminated when $\hat{\beta}_{a+1} \cong \hat{\beta}_{a}$.

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