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Statistical analysis of gastrointestinal transit time of pharmaceutical formulations

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The rate of movement of dosage forms through the gastrointestinal tract may influence the absorption of a drug, especially when it is absorbed over a limited region of the intestine. Hence reports such as that by Christensen et al (1985), which studied the influence of the type of dosage form on transit through the gastrointestinal tract, provide valuable information. However, examination of their results shows that wide variability occurs both between and within dosage forms in different subjects and because of small subject numbers there is difficulty in interpretation of the data. From their results, Christensen et al (1985) concluded that there was no significant difference between the transit time of a solution and small pellets in the series of experiments undertaken, but alternative interpretations are possible in the circumstances.

The type and extent of the statistical analysis performed and the exact meaning attached to 'significant' as used within the discussion and implied in the summary by Christensen et al (1985) require clarification. The difficulty in interpreting an appropriate statistical significance test, especially with low sample numbers is fully appreciated. From the context of their paper, a statistical significance would seem to be implied but the method of analysis is not clear. Therefore, the values of T 50% as shown in their Table 1 have been reanalysed to provide a comparison of solutions and pellet formulations. The given values of T 50% i.e. (1) gastric emptying time, (2) arrival at the caecum and (3) the derived value of transit through the small intestine, were assessed by three methods. The first method was Student's *t*-test, ignoring the matching of data (volunteers 3, 4, 5) and assuming all the data were independent and unmatched. However, this may not be taken to be a valid assumption as matched pair data should be analysed differently from unmatched data. The second and third methods take this difference into account, the third method being the same as the second but with a $\log_{10}$ initial data transformation to minimize the influence of the extreme values. The details of the second method are given below. The data for solution (A) or pellet (B) were separated into matched and unmatched groups; volunteers 3, 4 and 5 having taken both preparations, were matched and therefore separated (Group 1) from those volunteers who took either the solution (1, 2) or the pellet (6–10) (Group 2) and therefore were unmatched.

Group 1

For matched pair data, the mean difference ($\bar{d}_1$), standard deviation of the differences (s_1), and the estimated standard error of the mean of the difference, est s.e. ($\bar{d}_1$), is calculated

$$\bar{d}_1 = \frac{\Sigma(x_A - x_B)}{n_1}$$

$$\text{est s.e. } (\bar{d}_1) = \frac{s_1}{\sqrt{n_1}}$$

Group 2

For the unmatched data, the differences of the means ($\bar{d}_2$), the standard deviation of the differences, s_2, and the estimated standard error of the means of the differences, est SE ($\bar{d}_2$) are calculated:

$$\bar{d}_2 = \bar{x}_A - \bar{x}_B$$

$$s_2^2 = \frac{\Sigma(x_A - \bar{x}_A)^2 + \Sigma(x_B - \bar{x}_B)^2}{(n_A - 1) + (n_B - 1)}$$

$$\text{est SE } (\bar{d}_2) = s_2 \sqrt{\frac{1}{n_A} + \frac{1}{n_B}}$$

The weighted average ($\bar{d}$) of $\bar{d}_1$ and $\bar{d}_2$ is then calculated using weights w_1 and w_2 which are proportional to the reciprocal of the squares of the standard errors of the mean:

$$w_1 = \frac{1}{\text{est SE}^2(\bar{d}_1)} \quad \text{and} \quad w_2 = \frac{1}{\text{est SE}^2(\bar{d}_2)}$$

$$\text{i.e.} \quad \bar{d} = \frac{w_1\bar{d}_1 + w_2\bar{d}_2}{w_1 + w_2}$$

which is distributed approximately normally with a Standard Normal Deviant (SND)

$$\text{SND} = \bar{d}\sqrt{(w_1 + w_2)}$$

The calculated results for the 3 methods of analysis are shown in Table 1.

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Table 1. Results of the three methods of analysis of data from Christensen et al (1985) comparing gastrointestinal transit of solutions and pellets.

	Assume all unmatched calculated values of t	Sig. level $P < 0{\cdot}05$	Matched and unmatched pairs. Approx. SND	Sig. level $P < 0{\cdot}05$	$\log_{10}$ matched and unmatched pairs. Approx. SND	Sig. level $P < 0{\cdot}05$
Gastric emptying	7·86 df = 11	s	7·93	s	7·40	s
Arrival at caecum	0·94 df = 11	ns	8·59	s	6·65	s
Intestinal transit	0·92 df = 11	ns	6·74	s	3·60	s

s = Significant (sig.); ns = not significant.

The results show that there is a statistical difference in the value of T 50% for the intestinal transit of solutions and pellets, when consideration is given to the results as 'matched pairs'. This would therefore lead to a conclusion different from that reached by Christensen et al (1985). However, it must be emphasized that no comment is made about the practical and clinical importance of such a result when drawn from a sample that is so small, but variability of the data should be of great interest and concern to all those involved in the study, formulation and usage of oral dosage forms, especially as these become increasingly sophisticated and more numerous in their variations. Clearly much more work of the type reported by Christensen et al (1985) is required to assist these developments.

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REFERENCES

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