This hypothesis appears to be consistent with the finding that TRH inhibition is often incomplete and also with the in-vivo observations describing a conspicuous effect of TRH when acid secretion is stimulated via a neural, centrally mediated pathway.

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Statistical analysis of gastrointestinal transit time of pharmaceutical formulations: comments on the letter by Devereux & Newton

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The letter by Devereux & Newton (1985) is a useful contribution since it highlights the problem of the statistical analysis of data from experiments where crossover and group comparisons are combined. Generally such a design should be avoided if possible but since data of this kind may be produced it is important to be able to perform an optimal statistical analysis.

We agree that it is incorrect simply to forget about the matched pairs and analyse the data by methods for comparing two independent samples. The method proposed by Devereux & Newton is known to be the optimal one, *but only if the standard deviations are known and the variables are normally distributed.* When the standard deviations are unknown but estimated with high precision, i.e. many degrees of freedom, the method would certainly still be satisfactory. However, in the actual case discussed, the standard deviation of the differences is estimated with only 2 degrees of freedom in the matched pairs case and this gives a very inaccurate estimate, a fact overlooked in developing the method proposed by Devereux & Newton.

The pitfall of ignoring the inaccuracy of the standard deviation estimates is probably as invalidating for the final result as that of ignoring the matched pairs!

Take as an example the figures for intestinal transit given by Christensen et al (1985). The three matched pairs give $t_1(2) = 7{\cdot}60$ which is statistically significant at the 5% level (two-sided test). The 2 + 5 unmatched pairs give $t_2(5) = -1{\cdot}08$ which is not statistically significant at the 5% level (two-sided test). The test statistic called SND proposed by Devereux & Newton is also a weighted average of these two t-values, thus

$$\mathrm{SND} = \frac{t_1 s_{d2} + t_2 s_{d1}}{\sqrt{s^2_{d1} + s^2_{d2}}}$$

where s_{d1} and s_{d2} are the estimated standard errors of d_1 and d_2 based on matched and unmatched pairs respectively.

Since $s_{d2} = 54{\cdot}4$ and $s_{d1} = 20{\cdot}5$, the t_1 value is given more than double weight as compared with the t_2 value, although t_1 has infinite variance whereas t_2 has a variance of 5/3 if $E(d_2) = 0$.

The variance of a non-central t variable with ν degrees of freedom and non-centrality parameter, δ is

$$V(t_\nu(\delta)) = \frac{\nu}{\nu - 2}(1 + \delta^2) - \left(\sqrt{(\nu/2)}\,\frac{\Gamma(\nu - 1)/2)}{\Gamma(\nu/2)}\delta\right)^2$$

see for example Johnson & Kotz (1970).

Another problem arises because the two estimates $\bar{d}_1 = 156{\cdot}0$ and $\bar{d}_2 = -58{\cdot}7$ seem to be statistically significant. If this is true it makes no sense to pool the two estimates at all.

Assessing the statistical significance of the difference between $\bar{d}_1$ and $\bar{d}_2$ is a comparison of means in two normal distributions, which is easily done if the standard

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Table 1. Details of pharmaceutical formulations, subjects and fed states

Study	Formulation	Size (mm)	Subjects	Label	Drug present	Fed states	Small intestine transit Times (h)	Mean (h)	s.e.m.	
S1	Solution-DTPA	—	M—5	^{99m}Tc	No	LB	3·45, 3·0, 4·0, 4·2, 5·8	4·1	0·55	Total
S2	Solution-DTPA	—	M—6	^{99m}Tc	No	LB	5·0, 3·2, 5·5, 3·4, 3·8, 4·7	4·2	0·5	solution
S3	Solution-DTPA	—	M—6	^{99m}Tc	Yes	LB	3·4, 2·5, 5·0, 2·9, 3·9, 4·2	3·5	0·45	n = 23
S4	Solution-DTPA	—	M—6	^{99m}Tc	Yes	LB	3·0, 5·5, 6·0, 4·0, 4·0, 5·0	4·5	0·5	Mean = 4·13 S.D. = 1·0
P1	Pellets	0·3–1·2	M—4	^{99m}Tc	No	FA	2·1, 3·6, 3·8, 4·0	3·3	0·35	
P2	Pellets – resin	0·5–1·8	M—6	^{111}In	No	FA	3·2, 2·1, 2·2, 3·5, 4·8, 4·1	3·3	0·4	
P3	Pellets – resin	0·5–1·8	F—5	^{111}In	No	FA	7·4, 4·8, 7·1, 6·2, 2·7	5·6	0·8	
P4	Pellets – resin	0·5–1·8	F—5	^{111}In	No	FA	2·3, 5·9, 1·9, 2·4, 4·9	4·2	0·8	
P5	Pellets	0·8–1·2	M—5	^{99m}Tc	No	VA	1·9, 2·5, 2·7, 3·3, 9·5	3·8	1·5	Total pellets n = 81
P6	Pellets – coated	0·7–1·0	M—8	^{99m}Tc	No	LB	2·0, 1·3, 3·0, 3·8, 4·1, 5·1, 5·7	3·4	0·5	Mean = 3·3 S.D. = 1·49
P7	Pellets – coated	0·7–1·0	M—4	^{99m}Tc	No	LB	2·2, 2·7, 1·7, 1·5	2·0	0·2	
P8	Pellets	0·7–1·2	M—6	^{99m}Tc	No	LB	2·1, 3·9, 4·0, 2·4, 1·8, 4·6	3·1	0·6	
P9	Pellets	0·6–0·8	M—8	^{99m}Tc	No	LB	2·0, 4·0, 2·0, 2·3, 3·8, 1·8, 2·8, 1·9	2·4	0·2	
P10	Pellets	0·8–1·2	M—6	^{99m}Tc	Yes	LB	2·5, 5·0, 5·3, 2·0, 2·3, 3·0	3·4	0·6	
P11	Pellets	0·6–0·8	M—8	^{99m}Tc	No	HB	3·8, 3·1, 2·0, 2·0, 3·9, 1·4, 2·4, 1·2	2·5	0·4	
P12	Pellets	0·8–1·2	M—6	^{111}In	Yes	HB	3·9, 4·3, 4·5, 3·5, 2·1, 3·8	3·7	0·35	
P13	Pellets – coated	0·7–1·0	M—4	^{99m}Tc	No	HB	2·3, 2·5, 3·2, 3·2	2·8	0·2	
P14	Pellets	0·7–1·0	M—6	^{99m}Tc	No	HB	1·8, 2·7, 2·9, 3·5, 3·9, 4·6	3·2	0·4	

M – Male; F – Female; FA – Fasted; LB – Light Breakfast; HB – Heavy Breakfast; VA – Varied Breakfast.

(i) The last three subjects in S1 are the first three in P6. (ii)The same subjects in S2 and S3, S4 and P10, P9 and P11, P8 and P14.

deviations are known or at least known to be equal. In cases, as at present, where the standard deviations are expected to be unequal—since they are intra- and inter-subjects, respectively—and both have to be estimated, it is known that an optimal test does not exist.

This so-called Fisher-Behrens problem has been subjected to much discussion in the statistical literature and is fundamentally the same as that mentioned earlier of comparing the solution and pellet formulations on both matched and unmatched data. It is therefore suggested that this problem is solved by an approximate *t*-test following the same method as that proposed for the solution of the Fisher-Behrens problem. Welch (1938) proposed a method where the inaccuracy of the estimated standard errors was taken into consideration by a proper adjustment of the degrees of freedom for the approximately *t*-distributed test statistic.

The papers by Welch (1947) and Aspin (1949) also give ideas that could form a basis for the solution of the combined matched pairs and comparison of two independent samples. Bhoj (1984) compares various methods proposed by himself and by others and a review of papers dealing with the problem is given.

An alternative, more pragmatic approach to the problem is to conduct more studies, as was suggested by Devereux & Newton (1986). This we have now done and data for 188 determinations of gastric emptying and intestinal transit in volunteers and patients given solutions, pellets and single units have been reported by us (Davis et al 1986). Data relevant to intestinal transit of solutions and pellets (a total of 104 determinations) are given in Table 1.

A thorough statistical analysis of the determinations, obtained in 18 different studies in 75 different subjects, reveals that the structure is so complex that none of the methods proposed so far is applicable.

Two subjects received solution in one study only, 44 received pellets in one study only, 6 received solution in two different studies, 14 received pellets in two different studies and 9 received solution in one and pellets in another study.

The appropriate statistical model appears to be a variance components model for the log-transformed intestinal transit times. The random components are subjects, studies and subject-study interaction, the latter being completely aliased with a within-study random variation.

The existence of a random study component of a substantial size complicates the analysis, and moreover, it weakens the power of test. Thus, even though the analysis of the 104 determinations shows no statistically significant difference between intestinal transit times, the study-to-study variation may have masked a possible difference. Further studies employing a more efficient experimental design seem to be needed to reach a clear conclusion.

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