STATISTICAL CONSIDERATIONS OF "RENAL FUNCTION AND METHOXYFLURANE ANAESTHESIA" BY McINTYRE AND RUSSELL[1]

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In a recent article by McIntyre and Russell[1] data were presented from a renal function study of eight dogs using methoxyflurane and a control anaesthesia. On the basis of some statistical tests, the authors concluded that, "There was no statistical difference between the changes in PAH clearance of the two groups at the end of the two hour period, but there was a difference between the changes in inulin clearance which occurred (p. 133)." We take the phrase "... but there was a difference between the changes in inulin clearance ..." in the above quote to mean that statistical significance was found in inulin clearance.

Because of increasing evidence suggesting the methoxyflurane anaesthesia may be involved in renal toxicity, we present in this paper a reanalysis of the data published by McIntyre and Russell. Our purpose is to apply an alternative statistical approach which could be used to identify pertinent variables involved in renal toxicity as well as to test specific hypotheses concerning the effect of methoxyflurane on renal functions.

Data Analysis

(1) The original data of McIntyre and Russell are presented in Table I.

In Table II, we have calculated the *t*-tests on the inulin and PAH clearance data and on the difference between Test 1 and Test 2.

Neither Test 1 nor Test 2 was significantly different between the two groups. However, in addition to a significant average decrease in inulin clearance, we have also found a significant decrease in PAH clearance for the methoxyflurane group.

(2) The analyses presented by McIntyre and Russell and the one in Table II above attempt to control for individual characteristic renal functions by computing differences between preliminary clearances and those obtained after treatment. An alternative approach, the analysis of covariance, will be presented below. The advantage of this method of estimating variability which may be due to experimental error is that it efficiently adjusts for the animal's "effect" and allows exact estimation of the treatment and regression parts of the model.

For example, as Table III indicates, both inulin and PAH clearances were found to be significantly different between the two treatments. For inulin clearance, the treatment effect was significant at the 0.076 level and for PAH clearance, the probability was equal to 0.049. If one were to accept only the 0.05 level of confidence, then the conclusions of McIntyre and Russell would actually be reversed, i.e. PAH clearance would be significant while inulin clearance would not be. However,

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TABLE I

	Inulin clearance ml/min/kg		PAH clearance ml/min/kg	
Control dog No.	Test 1	Test 2	Test 1	Test 2
1	2.39	2.29	5.51	5.76
2	2.86	3.35	5.53	6.79
3	2.54	4.23	7.45	8.04
4	0.018	0.139	0.017	0.49
Methoxyflurane dog No.				
1	3.20	2.53	7.64	5.23
2	1.88	1.94	3.63	3.89
3	2.76	2.60	8.14	6.84
4	3.27	2.45	5.88	4.89

TABLE II

	Inulin Clearance			PAH Clearance		
	Test 1	Test 2	Diff.	Test 1	Test 2	Diff.
Means:						
Control	1.952	2.502	0.550	4.627	5.270	0.642
Methoxy.	2.778	2.380	−0.398	6.322	5.212	−1.110
Standard Error of Mean	0.726	0.895	0.450	1.900	1.770	0.591
t-value	1.137	0.137	2.106	0.893	0.032	2.967
p-value* (2-tailed)			<.10			<.05

*$df = 6$.

TABLE III*

Measure	Source	Sum of squares	Degrees of freedom	Mean square	F-ratio
Inulin	Treatment	4.23327	1	4.23327	4.585†
	Regression	44.07323	1	44.07323	47.735‡
	Residual	5.53979	6	0.92330	
PAH	Treatment	4.31209	1	4.31209	6.051§
	Regression	201.64340	1	201.64339	282.976‡
	Residual	4.27549	6	0.71258	

*The statistical model for this analysis can be found in the Appendix.
†$p = 0.076$
‡$p < 0.001$
§$p = 0.049$

because of the small sample size, we feel that the tests of significance should be performed at the 10 per cent level, which results in significance for both inulin and PAH clearances.

The estimating equation for inulin clearance is: $Y = 0.82773t + 0.93497X$, where X and Y are the Test 1 and Test 2 values, respectively. For PAH clearance, $Y = 0.73423t + 0.95050X$. In both cases, $t = -1$ for methoxyflurane and $+1$ for the control group.

Appendix

For both inulin clearance and PAH clearance, the statistical model is as follows:

$$Y_{ij} = t_i + bX_{ij} + R_{ij}$$

for $i = 1, 2$
$j = 1, 2, 3, 4$

where

Y_{ij} is the Test 2 clearance of the j-th dog on treatment i
t_i is the treatment (methoxyflurane or control) effect, fixed
b is a covariate, or regression coefficient, fixed
X_{ij} is the Test 1 clearance of the j-th dog on treatment i, fixed
R_{ij} is the residual effect, random.

Summary

The data from a recent article by McIntyre and Russell on the effect of methoxyflurane anaesthesia on renal functions were reanalysed using an analysis of covariance. Results of this alternative approach indicate that both PAH and inulin clearance were significantly affected by the methoxyflurane anaesthesia. The regression equations for estimating the two clearance values and the model for the analysis of covariance are also given.

Résumé

Le but de cet article est de suggérer une façon de voir pour l'analyse des données où il faut contrôler les caractéristiques des réponses individuelles des sujets. En utilisant l'analyse de covariance sur les données publiées par McIntyre et Russell, nous avons réussi à démontrer qu'il est possible de sonder plus précisément l' "effet" du sujet. Les résultats de notre analyse indiquent que, en plus de la clearance de l'inuline, la clearance de la PAH était également changée de façon notable par l'anesthésie au méthoxyflurane. En plus de pouvoir vérifier les effets du traitement de façon plus précise, cette méthode procure également les équations permettant d'évaluer les deux clearances.

REFERENCE

1. McIntyre, J.W.R. & Russell, J.C. Renal Function and Methoxyflurane Anaesthesia. Canad. Anaesth. Soc. J., *18*: 131 (1971).

Sir:

Any investigation requires a competent statistician to assist in the planning, and to present conclusions that may be drawn from the results. Mr Sloboda and Dr Roberts have drawn attention to an alternative way of manipulating our data and thus perform a service for readers of this journal. However, it is not apparent that a more powerful statistical analysis improves interpretation of the physiological phenomena under consideration here.

Another aspect of data interpretation is the manner in which useful or interesting information can be concealed by calculations with the data from apparently similar biological experiments. This has been considered by Parkhouse[1] and due attention was paid to it in the text of the publication from which the data selected for comment was taken.

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1. Parkhouse, P. James. Experiments and reports. Clin. Pharm. & Therap., *10*: 597 (1969).