Gall stones induced by octreotide

EDITOR,—The beneficial effects of treatment with octreotide are accompanied by an increased risk of gall stones. Grant W Bigg-Wither and colleagues found that in 22 patients (13 of whom had acromegaly) octreotide increased the fasting gall bladder volume; they propose that this may predispose to the formation of gall stones.[1] We believe, however, that this is unlikely to be the main factor in the pathogenesis of gall stones induced by octreotide. We have measured fasting gall bladder volumes in nine acromegalic patients before and after octreotide and found no significant increase during treatment.[2] Furthermore, although the fasting gall bladder volume in 31 untreated acromegalic patients was 30% larger than that in normal subjects, we found only a minor increase in the prevalence of gall stones.[3]

Octreotide impairs contraction of the gall bladder in response to a fatty meal and increases the residual volume of the gall bladder. This might be expected to promote the formation of stones because of relative stasis of the gall bladder. The residual volume of the gall bladder in untreated acromegalic patients, however, is three times that of normal subjects and yet the increase in gall stone prevalence in these individuals is small.

Our data suggest that although a reduction in gall bladder emptying may well play a role in the formation of stones, an increased fasting gall bladder volume is not a major factor in their pathogenesis. Native somatostatin increases the cholesterol saturation in bile,[4] and we have found similar changes in acromegalic patients with gall stones associated with octreotide.[5] These observations suggest that changes in bile chemistry may be at least as important as motor dysfunction of the gall bladder in the pathogenesis of gall stones induced by octreotide.

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Renal transplantation in tuberous sclerosis

EDITOR,—In their editorial on new insights in tuberous sclerosis David W Webb and John P Osborne rightly emphasise that the outlook for many adult patients with the disease is not as poor as previously thought.[1] They point out that renal disease was the leading cause of death in a recently reported series of patients[2] but do not mention that renal transplantation can now substantially prolong survival of patients who develop end stage renal disease. Colleagues and I have reported the outcome of three patients with tuberous sclerosis given transplants at our centre and have reviewed an additional six previously reported cases. I summarise here the main findings of this study.[3]

Survival is excellent. Our patients (three women aged 27-46 at the time of transplantation) were fully rehabilitated, with the graft functioning 65 to 132 months after transplantation. In the four other reported cases for which follow up data are available the course was equally satisfactory, only one patient dying, from an infection unrelated to tuberous sclerosis.[3]

No manifestations of neurological disease were observed in any of the seven patients after renal transplantation. Neurological disease before transplantation was mild: six patients had suffered a minor form of epilepsy, and none was mentally retarded. Probably patients with mild neurological disease survive longer, allowing renal failure to develop. Interestingly, all the patients given transplants were female, a finding in keeping with the reported higher early mortality—usually from neurological complications—in male patients.[4] Renal cell carcinoma was found in one kidney removed before transplantation,[5] and nuclear abnormalities of cystic epithelial cells suggestive of malignant transformation were observed in a kidney removed at transplantation from another patient. The overall prevalence of renal cell carcinoma in tuberous sclerosis is 4%, which is higher than that in a control population.[6]

In conclusion, patients with tuberous sclerosis with end stage renal failure are good candidates for renal transplantation. Neurological disorders did not progress after transplantation in the reported cases. The probable small risk of neoplastic transformation of native kidneys, which might be potentiated by immunosuppressant drugs, warrants bilateral nephrectomy before or at the time of renal transplantation.

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Assessing observer variability

EDITOR,—In their review of methods for assessing observer variability in clinical measures Paul Brennan and Alan Silman recommend using the $\varkappa$ statistic and the limits of agreement when studying categorical and continuous variables, respectively.[1] I do not think that using the limits of agreement is the best method. Indeed, Bland and Altman described its use for method comparison studies—that is, experiments aimed at assessing the reproducibility of two well defined methods, say A and B.[2] The purpose of studies of observer variability is generally not to assess the reproducibility of the performance of two well defined observers, except perhaps in internal audit, but to evaluate the concordance of two among many potential observers—that is, to quantify the observer variability in general.

In the language of analysis of variance, both methods A and B are a fixed factor while both observers are a random factor. Moreover, the signs of the differences have to be considered in the comparison of both methods but are irrelevant in a study of variability between two, among possibly other, observers. For instance, if the difference between measurements obtained with methods A and B is x for one subject and $-x$ for another one the resulting mean difference to be considered for these patients should be zero in a method comparison study and $|x|$ in an assessment of observer variability. The method of limits of agreement, which takes the signs of the differences into account, is thus well suited to comparing two methods but not two observers, at least in the general case.

I think that a better way of assessing observer variability is to use the intraclass correlation coefficient, originally described by Bartko,[3] which is the proportion of the total variability accounted for by the variability among subjects. If it is high not much of the variability is due to variability in measurements of different observers; thus the reproducibility is high. The intraclass correlation coefficient may be estimated from the components of a two way analysis of variance, taking into account variability between subjects and variability between observers. In the particular case of only two observers, however, it may be directly computed by the formula

$$\frac{s^2(x)+s^2(y)-s^2(d)}{s^2(x)+s^2(y)+\bar{d}^2-(s^2(d)/n)}$$

where n is the number of subjects, $s^2(x)$ and $s^2(y)$ are the variances of measures for observers X and Y, and $\bar{d}$ and $s^2(d)$ are the mean variance of the differences between measures of both observers, respectively.[4]

Finally, the intraclass correlation coefficient is mathematically equivalent to the $\varkappa$ statistic used for categorical measurements,[5] which is the method that Brennan and Silman recommend for assessing observer variability in this situation.

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AUTHORS' REPLY,—We broadly agree with Jacques Jamart's comments about the value of the intraclass correlation coefficient and had made similar points in an earlier version of our paper. During the revision process we removed this to make the article clearer for a non-statistical readership. We differ with Jamart, however, on the appropriate use of this measure. Though he is correct in stating that the intraclass correlation coefficient is conceptually and mathematically equivalent to the $\varkappa$ statistic, it also suffers from the same disadvantage of interpretation. Specifically, as the intraclass correlation coefficient may be considered to be the proportion of variation due to the observers it depends on the absolute variability due to the subjects. The suggested method of calculating the limits of agreement does not suffer from such a dependence and therefore results in more meaningful measures.

The variability between observers may also be calculated from an analysis of variance approach with the observers being considered as random effects, and this is indeed appropriate when there are more than two observers. Using the limits of agreement, however, does not provide meaningful results for methods of measurement in which