Perspectives in Gastroenterology: General Discussion

Prof. Buchanan: Could you comment on the nutritional effects of octreotide in patients with fistula or the short bowel syndrome, particularly with regard to suppression of insulin, which is obviously an important nutritional hormone. Do you take any measures to replace insulin in this situation?

Mr. Scott: We measured serum glucose regularly during the fistula study and of course particularly in the people who were on TPN, but there was never any need for insulin replacement in this group of 16 patients.

Prof. Buchanan: Are you not planning to give insulin routinely?

Mr. Scott: No.

Dr. Nightingale: In the 1 patient we studied, the glycosylated haemoglobin remained normal. I have made no regular glucose measurements except on the first patient and we found no problems.

Prof. Bloom: How much anecdotal evidence is there for suggesting the use of octreotide in other diarrhoeas, perhaps those due to infection?

Mr. Primrose: We had a couple of patients who had ileal reservoirs formed for ulcerative colitis, who did not have a good functional result because of high stool frequency. Octreotide was of no help. In fact it made them worse.

Dr. Harris: Perhaps I could report the international experience with octreotide in the management of patients with AIDS-related diarrhoea who have failed to respond to conventional therapy. We have a response rate of about 25%. We have treated some very rare cases of idiopathic hypersecretory diarrhoea with the same results; basically 1 out of 4 responded.

Dr. Farthing: Were these AIDS patients in whom no specific pathogen was identified or were there a variety of causes?

Dr. Harris: In most cases no pathogen was identified, but the relevant investigations were not always performed because of the patient’s condition. However, there does not seem to be a relationship between the presence or absence of a pathogen and the response to octreotide.

Dr. Farthing: We have treated 1 patient with proven secretory small intestinal diarrhoea. We perfused the small intestine and know that it was in a secretory state, but we have no idea as to the cause, having excluded all of the usual diagnoses. She is extremely happy on octreotide and has been for several years. If we bring her into hospital and stop octreotide, the diarrhoea gets worse. So I think that octreotide does work in some idiopathic secretory diarrhoeas. It does not appear to work in cholera, unfortunately.

Prof. Bloom: I was about to say that our past year’s experience with cholera is negative. It is interesting that there are somatostatin receptors on the entero-cyte. One would therefore expect the possibility of a direct action, which might be antisecretory.

Dr. Farthing: Can I perhaps bring us back to a problem we must deal with in the future, namely study design. Clearly one of the controversial issues that has emerged today is the question of fistula and how we can design studies which are going to answer the very crucial question as to whether TPN plus octreotide is actually better than TPN alone.
Mr. Scott: If we could collect 120 fistula patients in one institution and standardize everything, other than receiving octreotide and not receiving octreotide, then we could provide a perfect answer to the problem, but the nature of the disease does not lend itself, certainly in terms of numbers, to that degree of centralization. We find that the kind of patient who comes for nutritional help at the Hope Hospital has already received extensive therapy to close the fistula. They represent a group who are heading towards a surgical closure of that fistula. We believe that the people best targetted for octreotide are those who fistulate very early on at their local hospital. Clearly we have little influence on the type of therapy that they are receiving; most of them have parenteral nutrition, some of them are completely nil by mouth, some have access to water, and some also have additional enteral supplementation. We think it would be very difficult to standardize therapy in these patients outside our institution.

Prof. Lennard-Jones (London): I think you will only obtain an answer if, first of all, the patients have surgical fistulae, secondly they have high-output fistulae, and thirdly your treatment is started early. You are really trying to see if octreotide reduces the time for which patients need treatment, and therefore you have to ask your colleagues at the peripheral hospitals to advise you as soon as they get patients with fistulae. I think you have to standardize the nutrition so that you can make some control observations – shall we say for 3 or 4 days – then all patients have parenteral nutrition, and then you compare octreotide with placebo. You might get an answer in this way, but I do not think you will otherwise.

Mr. Scott: What you say is the ideal, but it is very difficult to achieve.

Prof. Lennard-Jones: I suspect you will not get an answer unless you can do something of that sort.

Dr. Farthing: Perhaps we could move on and discuss the role of octreotide in the management of variceal haemorrhage. There are probably more patients in this area than in any of the other groups we have considered today and it is a condition with a high mortality. I wonder whether we are convinced by the information that we have heard today? Do we think octreotide is a reasonable treatment, has the right study been done, and do we think octreotide should be compared to other, less invasive treatments? What should octreotide’s relationship to sclerotherapy be? It would appear that the particular unit that has performed this work is using early balloon tamponade rather than injection sclerotherapy.

Dr. McKee: I think it would have been true 5 years ago that the unit where I worked at the Royal Infirmary in Glasgow would have chosen balloon tamponade as the initial treatment for varices. Now that we have acquired a great deal of experience in injection sclerotherapy, there is no doubt in my mind that if I am treating someone with bleeding varices, and I can see adequately to inject them, I will do so. I think even today there will be a large number of district general hospitals where an experienced sclerotherapist is not always available, so there will remain a need for emergency control of bleeding. Trials will be needed to investigate whether octreotide assists our ability to inject varices acutely, whether it makes injection easier, and whether it reduces the blood loss around the time of injection.

Dr. Farthing: Dr. Harris, what are the plans for the future?

Dr. Harris: In fact there are no immediate plans, although several investigators have approached us. I think the state-of-the-art management is sclerotherapy. However, octreotide could be useful
as a holding therapy before hospital admission if variceal bleeding is suspected. The patient
would receive a subcutaneous injection of a large enough dose to cover the period before full
resuscitation is undertaken. A trial should perhaps aim at evaluating the number of units of blood
required during that period prior to sclerotherapy. Octreotide could also be useful in increasing
the effectiveness of sclerotherapy by reducing the number of sessions and possibly continued for
a period of 5–10 days during that critical phase.
Mr. McMahon (Leeds): My experience of the management of bleeding varices is that a balloon
tamponade is used when the bleeding is life-threatening. One does not use it unless it is life-
threatening because the balloon itself can be life-threatening. In other words, I cannot see how
you can compare octreotide to balloon tamponade because, by the time you need to use balloon
tamponade, you can only use balloon tamponade. At a preliminary stage you could perhaps
compare sclerotherapy with octreotide, as was done in Liverpool, and one of the endpoints would
be the need to use balloon tamponade.
Dr. McKee: I think you are illustrating the problems of trials in bleeding varices. There is
enormous variation between the trials in entry criteria and that is where some of the problems
arise. If one looks at the studies which have compared tamponade, the differences in outcome
can largely be explained by the

investigator’s attitude to its use. If it is used in a centre by experts and used early, then it is
effective and there are few complications. If it is used by the less experienced as a last ditch
manoeuvre then the results are poor. In our hospital it takes a certain number of hours to arrange
to have the patient resuscitated, whereas an octreotide infusion can be set up instantly in casualty
and might be of help in reducing the transfusion requirements.
Mr. McMahon: You are absolutely right and I think octreotide has a valuable potential role, but
if you compare it to an inappropriate alternative treatment then its value will not be clear to
clinicians.
Dr. McKee: What do you think we should compare octreotide to?
Dr. Farthing: The obvious comparison would have been to compare octreotide with vasopressin
or terlipressin. This is a pharmacological holding operation. We do not think for one moment
that octreotide is going to produce sustained control of bleeding in the vast majority of patients;
there is a 50% success rate, which is what one would expect from vasopressin.
Dr. McKee: Maybe we could ask Dr. Jenkins about that, because that is indeed what his unit has
done.
Dr. Jenkins (Liverpool): We saw a much better response with somatostatin than we did with
vasopressin. We think the difference between our trial and
Prof. Carter’s trial and the other large published Spanish trial comparing vasopressin and
somatostatin is the bolus injection. If one looks at the portal pressure after the bolus injection of
somatostatin, it decreases dramatically and slowly builds up over about 24 h despite the
continuous infusion, in spite of steady-state circulating concentrations of somatostatin after
approximately 15 min. Therefore one never achieves as low a portal pressure with continuous
infusions as one does with a continuous infusion and bolus injections. We initially compared
somatostatin with vasopressin in the control of acute bleeding and we have gone on to compare
injection sclerotherapy with somatostatin. Because it has no side effects, I think that if you
incorporated a bolus dose in the treatment regimen and maybe increased the rate of infusions, the
trial to do would not be with vasopressin but with either somatostatin against octreotide or octreotide against injection sclerotherapy.

Dr. Harris: There are ethical considerations in implementing studies nowadays given that sclerotherapy is considered state of the art. I do not think we can justifiably withhold sclerotherapy. The question is, as we have indicated before, how fast can the patient receive sclerotherapy? The aim of the study would be to compare how patients do in that time, whether it is 12, 24 or 48 h, with and without octreotide therapy.