Gastro-Entero-Pancreatic Tumors

Gastro-Entero-Pancreatic Tumour

Proceedings of Somatostatin Analogues – Peptide Therapy in Action Symposium

Session I, January 9th, 1989
Hammersmith Hospital, London

Chairman and Guest Editor:
S.R. Bloom
MA, MD, DSc, FRCP, Professor of Endocrinology,
Royal Postgraduate Medical School, London

4 figures, 12 tables, 1990

KARGER

Digestion

Vol. 45, Supplement 1, 1990

This publication was sponsored by Sandoz Pharmaceuticals, UK
Edited by Current Medical Literature Ltd, London

S. Karger · Medical and Scientific Publishers
Basel · München · Paris · London · New York · New Delhi · Bangkok · Singapore · Tokyo · Sydney

Printed in Switzerland by Thür AG Offsetdruck, Pratteln
ISBN 3-8055-5202-5

Contents

DIGESTION

International Journal of Gastroenterology

Founded as 'Archiv für Verdauungskrankheiten' 1895 by I. Boas
Continued as 'Gastroenterologia' 1939–1967
Former Editors: P. Morawitz (1934–1936), R. Staehelin (1937–1943), A. Hurst (1940–1945), W. Löffler (1943–1961), Th.C. Hunt (1947–1967), N. Henning (1953–1962), B. Ihre (1953–1967), H. Bartelheimer (1963–1967), M. Demole (1963–1971), H. Kapp (1968–1970), R. Lambert (1972–1978)

Publication data: 'Digestion' is published 12 times annually. Volumes 45–47 with 4 issues each appear in 1990.

Subscription rates: Subscriptions run for a full calendar year. Prices are given per volume, surface postage included.

Personal subscription: SFr. 156.80, US$ 95.20. (Must be in the name of, billed to, and paid by an individual. Order must be marked 'personal subscription'.)

Institutional subscription: SFr. 224.–, US$ 136.00. (Regular rate.)

Airmail postage: SFr. 25.–, US$ 18.00. (Extra per volume.)

Microform subscription: SFr. 112.–, US$ 68.00. (Available exclusively to subscribers of the paper edition.)

Single issues and back volumes: Information on availability and prices can be obtained through the Publisher.

Subscription orders: Orders can be placed at agencies, bookstores, directly with the Publisher S. Karger AG, P.O. Box, CH – 4009 Basel (Switzerland) or with any of the following distributors:

Deutschland, West-Berlin, Österreich, Ost-Europa: S. Karger GmbH
Postfach 1724
D – 8034 Germering/München

France: Librairie Luginbühl
36, bd de Latour-Maubourg, F – 75007 Paris

Great Britain, Ireland:
S. Karger Publishers, 1 Torberry Drive
Petersfield, Hampshire GU 31 4HW

USA: S. Karger Publishers, Inc.
26 West Avon Road, P.O. Box 529
Farmington, CT 06085

India, Bangladesh, Sri Lanka:
S. Karger India Subscription Agency
B – 5/132 Safdarjung Enclave
New Delhi-110029

Japan: Katakura Libri, Inc.
36-9 Hongo 3-chome
Bunkyo-ku, Tokyo 113

Change of address: Both old and new address should be stated and sent to the subscription source.

Bibliographic indices: This journal is regularly listed in bibliographic services, including *Current Contents®*.

Advertising: Correspondence and rate requests should be addressed to the Publisher.

KARGER

Digestion
Printed in Switzerland

S. Karger AG,
Postfach, CH – 4009 Basel (Schweiz)

Erscheint monatlich;
pro Jahr 3 Bände zu 4 Heften

DIGESTION

Submission: 'Digestion' invites contributions concerning all aspects of the digestive tract and liver. Only original papers written in English are considered and should be sent to:

Prof. W. Creutzfeldt
Medizinische Klinik der Universität
Robert-Koch-Strasse 40
D-3400 Göttingen (FRG).

Manuscripts should be submitted in triplicate (with three sets of illustrations of which one is an original), typewritten double-spaced on one side of the paper, with a wide margin.

Conditions: All manuscripts are subject to editorial review. Manuscripts are received with the explicit understanding that they are not under simultaneous consideration by any other publication. Submission of an article for publication implies the transfer of the copyright from the author to the publisher upon acceptance. Accepted papers become the permanent property of 'Digestion' and may not be reproduced by any means, in whole or in part, without the written consent of the publisher. It is the author's responsibility to obtain permission to reproduce illustrations, tables, etc. from other publications.

Special Requirements:

1. Investigations Involving Human Subjects: 'Digestion' requires that investigations performed on human subjects have the prior approval of the institutional committee on human experimentation. Authors are required to submit a signed statement as to the date and details of the appropriate review. In countries where such mechanisms for approval do not exist, authors are required to submit a signed declaration that the research was carried out in accordance with the Helsinki Declaration.

A similar assurance is required to document that animal experimentation was performed under appropriate circumstances.

2. Statement for Authors Submitting Original Research or Case Reports: 'The enclosed manuscript . . .(Title). . . has been approved by me as well as by the responsible authorities at the institute where the work has been carried out.

I certify that none of the material in this manuscript has been published previously in any form and that none of this material is currently under consideration for publication elsewhere. This includes symposia and proceedings of meetings and preliminary publications of any kind except an abstract of 400 words or less.'

(To be signed by *all* authors)

3. The undersigned also confirm that they qualify for (co-) authorship according to the 'Uniform Requirements for Manuscripts' published in the guidelines of the 'International Committee of Medical Journal Editors' in 1988 as follows: Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is also not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author. Persons who have contributed intellectually to the article but whose contributions do not justify authorship may be named and their particular contribution described in the section 'Acknowledgements'. Such persons must give their permission to be named.

Arrangement:

Title page: The first page of each paper should indicate the title (main title underlined), the authors' names, and the institute where the work was conducted. A short title for use as running head is also required.

Key words: For indexing purposes, a list of 3-10 key words in English is essential.

Abstract: Each paper needs an abstract of up to 10 lines.

Small type: Paragraphs which can or must be set in smaller type (case histories, test methods, etc.) should be indicated with a 'p' (petit) in the margin on the left-hand side.

Footnotes: Avoid footnotes. When essential, they are numbered consecutively and typed at the foot of the appropriate page.

Tables and illustrations: Tables and illustrations (both numbered in Arabic numerals) should be prepared on separate sheets. Tables require a heading and figures a legend, also prepared on a separate sheet. For the reproduction of illustrations, only good drawings and original photographs can be accepted; negatives or photocopies cannot be used. When possible, group several illustrations on one block for reproduction (max. size 140 × 188 mm) or provide crop marks. On the back of each illustration, indicate its number, the author's name, and 'top'. Color illustrations are reproduced at the author's expense.

References: In the text identify references by Arabic numerals [in square brackets]. Material submitted for publication but not yet accepted should be noted as 'unpublished data' and not be included in the reference list. The list of references should include only those publications which are cited in the text. Do not alphabetize; number references in the order in which they are first mentioned in the text. The surnames of the authors followed by initials should be given. There should be no punctuation other than a comma to separate the authors. Cite all authors, 'et al' is not sufficient. Abbreviate journal names according to the Index Medicus system. (Also see International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. Br Med J 1988;296:401-405.)

Examples

(a) Papers published in periodicals: Kauffman HF, van der Heide S, Beaumont F, Blok H, de Vries K: Class-specific antibody determination against *Aspergillus fumigatus* by means of the enzyme-linked immunosorbent assay. III. Comparative study: IgG, IgA, IgM ELISA titers, precipitating antibodies and IgE binding after fractionation of the antigen. Int Arch Allergy Appl Immunol 1986;80:300-306.

(b) Monographs: Matthews DE, Farewell VT: Using and Understanding Medical Statistics. Basel, Karger, 1985.

(c) Edited books: Hardy WD Jr, Essex M: FeLV-induced feline acquired immune deficiency syndrome: A model for human AIDS; in Klein E (ed): Acquired Immunodeficiency Syndrome. Prog Allergy. Basel, Karger, 1986, vol 37, pp 353-376.

Full address: The exact postal address complete with postal code of the senior author must be given. If correspondence is handled by someone else, indicate this accordingly.

Further details: Authors may consult our leaflet 'Rules for the Preparation of Manuscripts', available on request from the Publisher, S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland).

Page charges: There is no page charge for papers of 5 or fewer printed pages (including tables, illustrations and references). Each additional complete or partial page is charged to the author at SFr. 295.- / US $ 195.00. The allotted size of a paper is equal to approx. 10 manuscript pages (including tables, illustrations and references). The inability to pay the additional page charge will not prejudice publication of the paper. This will be decided by the Editor.

Galley proofs: Unless indicated otherwise, galley proofs are sent to the first-named author and should be returned with the least possible delay. Alterations made in galley proofs, other than the correction of printer's errors, are charged to the author. No page proofs are supplied.

Reprints: Order forms and a price list are sent with the galley proofs. Orders submitted after the issue is printed are subject to considerably higher prices. Allow five weeks from date of publication for delivery of reprints.

Contents

Digestion 1990;45(suppl 1):5–10

0012–2823/90/0457–0005$2.75/0

Sandostatin and the Hammersmith Experience

D. Wynick, S.R. Bloom

Department of Medicine, Hammersmith Hospital, London, UK

Key Words. Pancreatic islet cell tumours · Sandostatin · Octreotide · Hammersmith Hospital

Abstract. Ten patients with various metastatic pancreatic tumours have received Sandostatin (octreotide) for up to 5 years, initially 50 μg t.i.d. subcutaneously but increased over 6–12 months to 500 μg t.i.d. Three patients showed no biochemical or clinical response to Sandostatin. In the remaining patients, treatment was extremely effective: tumour secretions fell by nearly 60% and clinical symptoms improved or resolved in all. At 5–6 months, all patients showed worsening symptoms and rising hormonal concentrations. Although relapses were initially responsive to Sandostatin (at 500 μg t.i.d.), patients eventually became unresponsive to all therapies, and all died within 6 months of the development of this resistive phase. Side effects were minimal and long-term therapy was well tolerated. Steatorrhoea and the development of gallstones were not observed.

Pancreatic islet cell tumours have a number of features in common. First, they are all extremely rare: the insulinoma has an incidence of $1/10^6$ in the UK population, while the incidence of vipoma and glucagonoma is as low as $10–15/10^6$. These tumours are also slow growing, with a natural history of between 1 and 2 decades, and they cause ill effects through excessive secretion of biologically active products rather than by tumour burden [1, 2] – although this does occur late in the disease. Many patients have metastases at presentation and treatment is therefore palliative; exceptions to this are the insulinoma, where approximately 90% of cases are benign, and those tumours associated with multiple endocrine neoplasia type 1, where approximately 40–50% are benign.

The objective of therapy is 2-fold. Firstly, to reduce the tumour mass, which can be achieved by surgical debulking [3], hepatic artery embolization [4], and cytotoxic chemotherapy – in this unit we favour a combination of streptozotocin and 5-fluorouracil [5]. Secondly, to reduce the secretion of tu-

Table 1. Patient characteristics before and during Sandostatin therapy

Patient	Hormones secreted	Hormone level before treatment pmol/l	Hormone level 1 month after starting treatment pmol/l	Hormone level last admission before death pmol/l	Months on Sandostatin
1	glucagon	280	170	1,064	28
	gastrin[1]	42	38	200	
2	VIP	276	291	324	< 1
	glucagon	222	215	267	
3	VIP	248	11	139	24
4	glucagon	400	288	1,113	13
5	VIP	309	324	330	< 1
	gastrin[1]	43	13	437	
6	VIP	447	16	222	26
7	glucagon	165	220	342	< 1
8	glucagon	2,160	1,561	> 10,000	35
	PP	9,570	2,290	> 10,000	
	gastrin[1]	6	8	142	
9	VIP	320	253	359	54
	neurotensin	1,000	250	1,030	
	glucagon[1]	17	8	980	
10	VIP	180	50	657	36

[1] Hormone level became elevated subsequent to initial diagnosis.

mour products. Native 14 amino acid somatostatin has potent antisecretory properties in such patients [6], but it suffers the major disadvantage that it has to be given by intravenous infusion and has a half-life of only 2.5–3.5 min. This is obviously unacceptable for all long-term ambulatory therapy. In the long-acting somatostatin analogue, Sandostatin (SMS 201–995, octreotide; Sandoz Pharmaceuticals), which has a half-life of approximately 113 min and is well absorbed when given subcutaneously, we have a useful drug of proven therapeutic value [6–10]. Sandostatin has been in use for approximately 5 years for the treatment of pancreatic islet cell tumours, and I report here our experience at the Hammersmith Hospital.

Patients and Methods

Ten patients with various metastatic pancreatic tumours were treated with Sandostatin for up to 5 years. Many of the patients had more than one elevated hormonal level at the time of diagnosis (see table 1). Some had one predominant syndrome, while others had a mixed clinical picture. Four of the patients (those starred in table 1) developed other hormonal elevations, with new associated syndromes, months or years after their original diagnosis. Sandostatin was given subcutaneously, initially 50 µg t.i.d., then increased over 6–12 months to 500 µg t.i.d.

Results

Three patients (No. 2, 5, and 7) responded neither biochemically nor clinically to the analogue after 3–4 weeks' therapy. We were unable to determine why this was so, although all 3 of these patients presented extremely late in their disease with huge tumour bulk and all died within 4–5 months of diagnosis. The remaining 7 patients were treated with the analogue for a mean of 29 months, with a range of 13–54 months. Treatment was extremely effective in each of these patients. Tumour secretions fell by nearly 60%, although in only 1 patient did the secretions actually fall to completely within normal limits. The clinical symptoms improved or resolved in all patients. In the patients with vipoma the number of bowel motions fell and stool consistency improved, while in the patients with glucagonoma the skin rash resolved more quickly and recurred less often. This clinical and biochemical improvement was maintained in all cases for at least 2 months and in 1 patient (No. 2) for up to 6 months.

All patients showed a good clinical response for the first 2 or 3 months of Sandostatin therapy. Thereafter, at approximately 5–6 months after starting therapy, all patients suffered exacerbations of their disease with worsening symptoms and rising hormonal concentrations. This relapse was initially responsive to an increase in dose of Sandostatin. However, after an average of 24 months at maximal dosage (delineated as 500 µg t.i.d.) these relapses were no longer responsive to a further increase in dose of Sandostatin or to other therapeutic measures, including hepatic artery embolization and chemotherapy. Once this resistant phase of their illness was reached, all patients died within 6 months.

Figure 1 shows the course of patient 2. Despite an extremely potent fall in vasoactive intestinal peptide (VIP) initially, the dose of Sandostatin had to be increased over the next 18 months to 500 µg t.i.d. to maintain stool frequency at less than 3 bowel motions/day. During this time VIP again rose to pre-diagnostic levels.

Side Effects

Side effects were minimal. The mean fasting blood glucose did not alter during therapy and, apart from some local skin irritation which lasted under 1 min, long-term treatment was well tolerated. The side effects one might expect – steatorrhoea and the development of gallstones – were not seen. However, many of the patients, particularly with the vipoma, had diarrhoea already and steatorrhoea might therefore have been masked. We have not yet observed the development of gallstones in such patients, although this is now reported in the literature; it may be that, as the analogue becomes more widely used for longer periods of time, this will become a more common phenomenon.

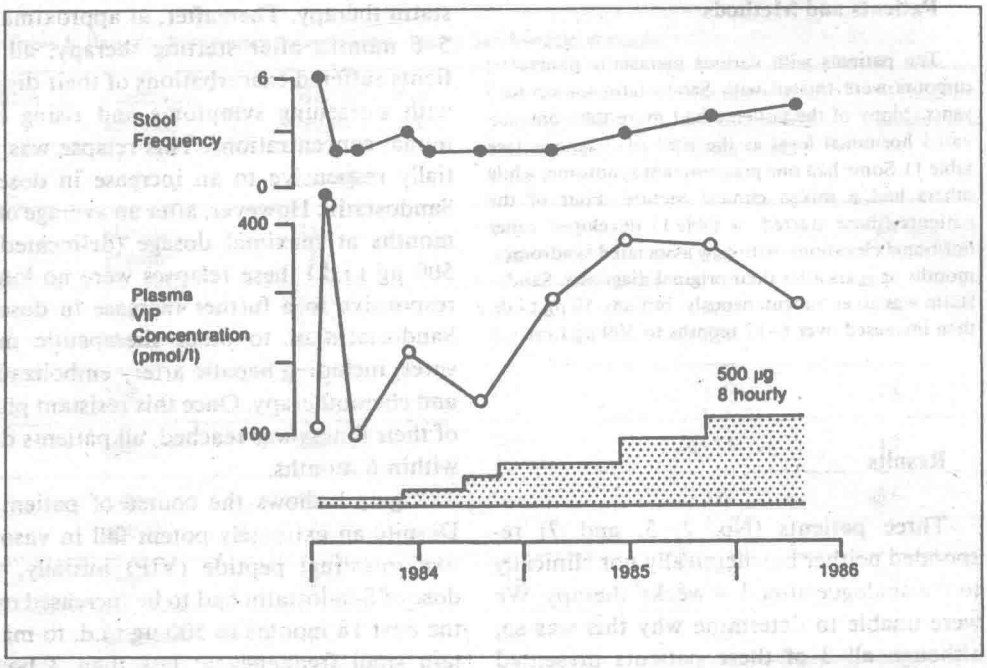

Fig. 1. Long-term course of patient 2 on Sandostatin therapy – stool frequency and VIP concentration.

Discussion

This study demonstrates that, for many patients with metastatic pancreatic endocrine tumours, initial palliation is satisfactorily achieved with Sandostatin. Three patients did not respond to Sandostatin, presumably because they had such extensive metastases at the time of diagnosis that they fell into the 'resistant' category of patients. The phenomenon of resistance we feel is mainly explained by large tumour bulk at a late stage of the disease and also possibly by a loss of responsiveness of the tumour through a decrease in the numbers of somatostatin receptors on the tumour cell surface.

We have also found Sandostatin to be extremely effective when given prior to chemotherapy or hepatic artery embolization to prevent the huge release of tumour products 7–14 days after therapy, thus avoiding the risk of a vipoma or carcinoid crisis with hypotension and possible death. To place the patient prophylactically on Sandostatin at a dose of 500 µg t.i.d. eliminates this problem completely.

References

1 Friesen SR: Tumours of the endocrine pancreas. N Engl J Med 1982;306:580–590.

2 Sabate MI, Carlei F, Bloom SR, Polak JM: Endocrine tumours of the gut and pancreas; in Polak JM, Bloom SR (eds): Endocrine Tumours. The Pathology of Regulatory Peptide-Producing Tumours. Edinburgh: Churchill Livingstone, 1985, pp 193–208.

3 Bauer W, Briner U, Doepfner W, et al: A very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982; 31:1133–1140.
4 Allison DJ: Therapeutic embolization. Br J Hosp Med 1978;20:707–715.
5 Moertel CG, Hanley JA, Johnson LA: Streptozotocin alone compared with 5 fluorouracil in treatment of advanced islet-cell carcinoma. N Engl J Med 1980;303:1189–1194.
6 Ch'ng JLC, Anderson JV, Williams SJ, Carr DH, Bloom SR: Remission of symptoms during long term treatment of metastatic pancreatic endocrine tumours with long acting somatostatin analogue. Br Med J 1986;292:981–982.
7 Anderson JV, Bloom SR: Neuroendocrine tumours of the gut: Long-term therapy with the somatostatin analogue SMS 201–995. Scand J Gastroenterol 1986;21(suppl 119):115–128.
8 Kraenzlin ME, Ch'ng JLC, Wood SM, Carr DH, Bloom SR: Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible skrinkage of metastases. Gastroenterology 1985;88:185–187.
9 Wood SM, Kraenzlin ME, Adrian TE, Bloom SR: Treatment of patients with pancreatic endocrine tumours using a new long-acting somatostatin analogue: Symptomatic and peptide responses. Gut 1985;26:438–444.
10 Williams NS, Cooper JC, Axon ART, King RFGJ, Baker M: Use of a long acting somatostatin analogue in controlling life threatening ileostomy diarrhoea. Br Med J 1984;289:1027–1028.

D. Wynick
Department of Medicine
Hammersmith Hospital
London W12 0NN (UK)

Discussion

Dr. Glaser: What is the highest dosage that you have used in patients with large tumour bulk?

Dr. Wynick: We have gone up to 1,000 µg t.d.s – total 3,000 µg/day – but as I said, at this late stage where we have resistance, we have found that this high dose has no greater effect than 500 µg t.d.s.

Dr. Glaser: Have you tried administering Sandostatin by continuous subcutaneous infusion?

Dr. Wynick: We have not, but we have tried giving Sandostatin intravenously and again have found no further effect.

Prof. Bloom: Your final conclusion then, David, is that you actually do have true escape?

Dr. Wynick: Yes.

Dr. Glaser: We have given Sandostatin by continuous infusion and feel that we do have a better response if we give somewhat higher doses. However, our results are very similar to yours once you reach the stage of resistance. Even with a dose as high as 5,000 µg/day we may see a little better response, but no marked improvement.

Question: Have you looked at any of the tumour material of patients with escape? Have they receptors?

Prof. Bloom: You are asking the very reasonable question: is this escape the result of a very strong agonist effect which cannot be overcome with antagonists or is it down-regulation?

Dr. Wynick: Sadly, I cannot give you the answer. Some of our patients died at home. Of those who died in hospital, the relatives quite reasonably refused to allow us to investigate.

Question: With these large doses, do you get evidence that other, normal tissues have become resis-

tant to somatostatin? For example, are growth hormone and insulin totally flat?

Dr. Wynick: Growth hormone certainly is almost completely flat. As I have said, you would expect these patients to have hyperglycaemia and to run into problems with diabetes but we do not, so I assume there must be the phenomenon of receptor down-regulation.

Prof. Bloom: So, there is a form of escape which is obviously related to down-regulation, but it is difficult to know whether this is due to continued administration of Sandostatin or whether it occurred right from the beginning, say within the 1st week. One of the obvious pieces of natural evidence in this area is the behaviour of the somatostatinomas, where interestingly you can see patients who have had diabetes mellitus for 15 or 20 years (we had one case with a 20-year history) and the moment that tumour is removed the diabetes disappears. This is strong evidence in our opinion that there may be escape of a biological sort but no eventual complete down-regulation of the receptors. It is not like LHRH where, if you give a large amount, you completely abolish the receptors.

Question: Was there any evidence of temporary tumour regression?

Dr. Wynick: You mean in terms of actual decrease in size of the liver metastases? Yes, we have seen that from time to time, but as I am sure you are aware, the terrible difficulty is that when you have such large vascular tumours they often outgrow their own metastases and you get spontaneous autonecrosis. In this unit we initially described – I think it was the first case – an excellent clinical response and a CT response, but we later found that that was not the case. Personally, I feel that a regression of tumours does not normally occur with Sandostatin, certainly not long-term.

Prof. Bloom: To reiterate that point, we are drawing on the evidence of our publication in *Gastroenterology* [8] which suggested that hepatic metastases from a VIPoma disappeared on treatment with Sandostatin. We think probably there was some tumour shrinkage, but much of the effect we saw was due to a change in the blood flow of the secondaries, so that they became isodense and could no longer be clearly seen on the CT. If one looks at such tumours in echos they are indeed reduced, as in this patient, but this could easily be due to infarction, to changes in blood flow or, as said earlier, perhaps to a spontaneous change, and our general experience is that the tumour size is not reduced significantly, if at all. What is not clear is whether the rate of enlargement of the tumour is slowed, because we know from biological studies in animals that somatostatin is definitely inhibitory to growth of normal tissues, such as the mucosa of the stomach and of the pancreas, under certain circumstances. There is a potential for tumour stasis and that may be biologically important, but so far I have not seen any very clear evidence of that.

Question: Can you tell us what serum levels of compound you achieve at high dose rates?

Prof. Bloom: High levels. They are proportional. We have not seen any enhanced rate of clearance, if that is what your question implies. If you give twice as much, as far as I am aware, you get twice the blood level. There is no tendency for hepatic or renal clearance either to be flooded or to upgrade.

Digestion 1990;45(suppl 1):11–16

0012–2823/90/0457–0011$2.75/0

Sandostatin and the Belfast Experience

K.D. Buchanan, J.S.A. Collins, A. Varghese, C.F. Johnston, C. Shaw

Institute of Clinical Science, Queen's University, Belfast, UK

Key Words. Apudomas · Sandostatin · Queen's University of Belfast

Abstract. Twenty-four patients with 26 apudomas have been treated with Sandostatin (octreotide) in Belfast. The 2 patients with vipoma showed an excellent response clinically and biochemically. Of 15 patients with carcinoids, Sandostatin improved the diarrhoea in 70%, flush in 58%, and wheeze in 100% of patients. Patients with insulinoma and the Zollinger-Ellison syndrome were unresponsive to Sandostatin. In general, the response to Sandostatin appeared to decline as the tumour size increased and tumour markers rose. Side effects have not been a problem.

Incidence of Apudomas

In Northern Ireland, which has a population of 1.5 million, we maintain a register of apudoma patients [1, 2]. Table 1 shows the incidence of apudomas in this population. We expect approximately 1 insulinoma/10^6 of the population/year and slightly less for gastrinomas. Tumours like vipomas and glucagonomas are rare, whereas carcinoid tumours are much commoner. Table 1 summarizes the percentages of the different types of apudoma which we have encountered.

Natural History of Apudomas

Apudomas frequently grow slowly and patients may have extensive metastases and yet remain relatively well, unless they are symptomatic with an endocrine syndrome. Some of the tumours are 'quiet' hormonally and do not cause great disturbance, and possibly Sandostatin would not be indicated in such patients. An awareness of the natural history of these patients is important before we decide on therapy and should also be taken into account when assessing therapy. For example, 2 of our patients, despite hav-

Table 1. Apudomas in Northern Ireland

Syndrome	Annual incidence per population of Northern Ireland	Each type %
Carcinoids	15.0	79
Insulinomas	1.8	9
Zollinger-Ellison syndrome	0.75	4
VIPomas	0.18	1
Glucagonomas	0.18	1
Unknown types	1.05	6
Others	negligible	

Table 2. Apudomas treated with Sandostatin (26 syndromes in 24 patients)

Syndrome	Number
Carcinoids	15
Insulinoma	2
VIPomas	2
Zollinger-Ellison syndrome	4
Unknown type	1
Medullary cancer of thyroid	1
Nesidioblastosis	1

ing extensive metastases, have survived with good-quality life-styles. A female patient with the carcinoid syndrome complains of some facial flushing which is not disturbing but has no other problems; although she has extensive metastases, she has lived happily in this state for years and for this reason we have not administered any therapy. Another female patient with a carcinoid tumour with extensive metastases was diagnosed following laparotomy for a gun-shot wound. She has remained well for several years and there has been no evidence of further growth of the tumour. Her syndrome, which is quite mild, appears to have resolved, yet she has had no treatment at all.

Patients Treated

Table 2 shows the number of patients we have treated over recent years with Sandostatin. The number of syndromes outnumbers the number of patients because some patients have more than 1 syndrome. Many of the patients self-inject themselves just as a diabetic patient does on insulin treatment. They can increase or decrease their dose and can monitor their response themselves. Some patients have had Sandostatin only acutely, either because it was ineffective or because other therapy was preferred. Five patients have received the drug for more than 2 years and we have detected no fall-off in effect. It is difficult to produce an objective assessment of response. If there was no change in symptoms we awarded a rating of 0%, if there was a distinct improvement we awarded 50%, and if the patients were virtually symptom-free 100% was awarded. If there were several symptoms, the assessments were averaged to give an overall response.

Gastrinomas, Vipomas, Insulinomas

We have only a small experience of the use of Sandostatin in gastrinoma patients. In 1 patient who received Sandostatin acutely, circulating gastrin was suppressed into the normal range. Sandostatin could therefore be useful in this patient. However, patients with gastrinomas are controlled effectively by alternative management, especially by potent drugs which inhibit acid secretion. Another patient with a gastrinoma who also

suffered from Cushing's syndrome had massive circulating levels of plasma gastrin, and Sandostatin on this occasion had no effect.

The diarrhoea of the watery diarrhoea hypokalaemic achlorhydric syndrome is described like milky tea and is odourless, watery, and very profuse. Such patients are extremely dehydrated and very ill. They may be diagnosed as having pancreatic cancer and extensive metastases and many may die before the clinician realizes the correct diagnosis. This may possibly be the reason why there is an apparently low incidence of patients with this syndrome. The 2 patients whom we have treated have both shown a superb response to Sandostatin. In 1 patient we noted the plasma VIP levels fell immediately to normal levels during Sandostatin administration [3]. Interestingly, when we stopped Sandostatin there was continued suppression of the VIP levels and continued cessation of symptoms, which suggested that Sandostatin was probably still present on receptor sites on the tumour.

We gave Sandostatin to a single case of insulinoma. The insulin levels following oral glucose were suppressed with Sandostatin, although this may have been an effect on intestinal absorption of glucose. However, unfortunately the patient had more hypoglycaemic attacks on the drug than off it.

Carcinoids

Table 3 demonstrates the response in carcinoid patients. In the majority of patients the primary site is the lower small intestine, but we also have encountered a number of lung carcinoids, and for some the primary site is unknown. I do not believe statistics would show that the responses differ between the different primary sites, although it is likely that tumours from different sites do produce different peptides. It may be, as the numbers increase or as we have multicentre information, that a differential response will be shown for the tumours at different primary sites. It is my impression that the lung carcinoids respond better.

Table 3. Effects (%) of Sandostatin in 15 patients with carcinoids

Symptoms	No change	Better	Much better
Diarrhoea (n = 15)	20	27	43
Flush (n = 12)	42	50	8
Wheeze (n = 2)	0	0	100

In the carcinoid patients there are three major symptoms which we attempt to treat – the diarrhoea, which is watery and disabling; the flush, which is troublesome only in a few; and the wheeze, which is a less common feature of the syndrome. In about half the patients the diarrhoea cleared on Sandostatin treatment, whereas the effects on the flush appeared to be less. In the 2 patients who wheezed, Sandostatin appeared to be very effective. In 1 patient with a very extensive, very aggressive tumour, who died after a few months, the response to Sandostatin was poor and there was apparently only a modest effect on the circulating tumour marker. Another patient with the carcinoid syndrome had a very extensive tumour with both flushing and diarrhoea, as well as an advanced cardiac lesion, so the prognosis appeared poor. This patient was treated by Sandostatin, intrahepatic chemotherapy, and interferon (Intron A). There was a dramatic reduction in tumour mass, circulating tumour marker, and symptoms. However, because we were using multiple treatments it