Somatostatin in Digestive Diseases: Improving the Treatment Options

Guest Editor

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11 figures and 31 tables, 1999
Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.
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As a general rule, philosophically, standing back and taking a look at where we are and what we are doing in a particular field is often commended to us as a good strategy for assessing progress. It is difficult enough when considering just one topic, but very much more difficult in the present case of somatostatin usage as this hormone’s actions are protean! Professor Scarpignato and his colleagues deserve great thanks for tackling this task so successfully and navigating well in tricky waters.

When I was asked to write this foreword, little did I anticipate that it would be an exciting and updating experience to read the excellent papers in this volume. There can be very few emergencies in the practice of gastroenterology, which are more taxing to both primary care teams and specialist physicians and surgeons in hospitals, than upper gastrointestinal hemorrhage. Traditionally, serious upper gastrointestinal hemorrhages, both variceal and nonvariceal, used to come to the surgeons. What a dramatic change has occurred over the last 20 years, especially, for example, in the management of variceal hemorrhage with control of approximately 90% of cases of acute variceal hemorrhage by emergency endoscopic injection. Of course, there are several other ably reviewed techniques available as well. Studies combining pharmacotherapy with vasoactive drugs, in conjunction with sclerotherapy, point the way to improvements, and instituted early should lead to future better strategies in this condition. There is more than a hint that primary care groups should be involved in their early administration where a high index of suspicion exists. Readers will be impressed by the scholarly reviews here presented in orderly and timely fashion, reflecting much good clinical science and reminding clinicians of the fascinating aspects of basic science relating to this peptide. The focus in this issue on the use of native somatostatin as a prime element in therapy reminds me of Shakespeare’s words, ‘holding a mirror up to nature’. Are the pharmacologists doing that very thing? Clearly, not for the first time, has a natural product been shown to be of immense therapeutic value. We only have to remind ourselves of insulin and cortisone as other examples. So, we may herein have a case of history repeating itself in using one of man’s naturally occurring substances to treat different groups of man’s afflictions. The many actions of somatostatin are well set out in the review by Professors Scarpignato and Pelosini who rightly emphasize the wide-ranging clinical therapeutic potential of this ubiquitous hormone.

The story of somatostatin is indeed an intriguing one with more data being added each year, but I was surprised to be reminded that it is 26 years since the hormone was, in fact, recognised. While several synthetic analogues are much more stable than the native peptide none incorporate all of the natural peptide’s range and subtlety of actions. Teasing out the best method of administration, timing and specific dose of analogues or natural peptide form the meat of some of the reviews and clearly have demanded the dedication and precision of many investigators often in patients with highly unstable hemodynamics.
Many clinical enigmas remain. For example, why do repeated bolus injections of somatostatin appear to be more effective than continuous infusion in variceal bleeding? As many of the authors emphasize, the wide spectrum of somatostatin activities would require simultaneous use of several different pharmacological agents, and one speculates that such a cocktail would fail to mimic the actions of a natural peptide with the added and unwanted burden of unacceptable side effects of polypharmacy. In Goulis and Burroughs’ review, the technique of data analysis of several studies is aided by the use of appropriate statistics helping us to see more clearly the picture presented by several reports of varying design and endpoints. Others review the controversial issues of digestive tract fistulas and their therapy, highlighting how difficult it is to do randomized controlled trials in such cases. Readers will be pleased to see that randomized controlled trials strongly suggest a benefit of somatostatin in preventing complications after pancreatic surgery, but the picture is not yet clear in high-risk patients with upper gastrointestinal tract bleeding or in some cases of persistent pancreatic fistulas.

This volume is greatly enhanced by the contribution of colleagues from Créteil, France. Prof. Fagniez and Dr. Yahchouchy report on pharmaco-economic issues surrounding the use of somatostatin in the treatment of digestive fistulas. They rightly highlight the importance of this issue in all countries where health care budgets are under scrutiny by politicians and economists alike, astutely deducing that somatostatin can save up to 40% of the global costs of treatment of digestive fistulas. They wisely make a plea for inclusion of economic data in randomized controlled trials to address the cost-effectiveness issue in future studies.

This volume focussing on somatostatin in digestive diseases will educate many doctors, bringing most right up to date, stimulating others to go out and do more research, and should be compulsory reading for all clinicians, including trainees whether medical or surgical in the field of gastroenterology. The editor and his team are to be congratulated.

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Acute bleeding from varices in the esophagus is a catastrophic complication of portal hypertension and has posed a persistent and often frustrating challenge to gastroenterologists, endoscopists, surgeons and general practitioners alike for more than half a century. Upper gastrointestinal (UGI) bleeding which is nonvariceal in origin can arise from a number of conditions including peptic (gastric, duodenal, 'stress' and iatrogenic) ulcers, gastric erosions, pertussis hyperglobulinemia and cancer. Although this bleeding ceases spontaneously in approximately 80% of cases, both kinds of bleeding represent life-threatening conditions whose mortality, especially in high-risk patients, remains high. The management of patients presenting with UGI (variceal and nonvariceal) bleeding involves resuscitation to restore normovolemia and stabilize vital signs, endoscopic diagnosis of the source of hemorrhage, and the initiation of appropriate medical therapy. Since there might be a delay between the onset of UGI bleeding and endoscopic diagnosis and therapy, pharmacotherapy is the only therapeutic option to secure rapid hemostasis as it can be administered immediately on admission to hospital without the need for specialized expertise. Although no drug is capable of safely and permanently occluding a spurting varix or a bleeding ulcer, an agent capable of promoting rapid hemostasis would be advantageous in the management of UGI bleeding, as it could be administered before endoscopy. Control of bleeding before endoscopy has the advantage of reducing the risk of aspiration pneumonitis and improving visualization, thereby facilitating a differential diagnosis and endotherapy. The pharmacological treatment, however, must be extremely safe in such clinical situations since patients with UGI bleeding are frequently in an unstable hemodynamic condition and may have severe underlying liver disease that should not be further deteriorated by inappropriate drug use. These 'emergency medications' should therefore be devoid of undesirable effects and of drug-to-drug interaction, an important consideration in critically ill patients who are usually polymedicated.

Up to 80% of patients with acute pancreatitis suffer from a mild and self-limiting disease which responds well to conservative treatment without any specific medication. Morphologically, this form of the disease is characterized by edema in and around the pancreas, and peripancreatic fatty tissue necrosis may occur. The other 20% of patients display a rapid, clinically severe course with pancreatic parenchymal and extrapancreatic necroses. While both the complication and mortality rates in edematous acute pancreatitis are low (<1%) patients suffering from the necrotizing form develop systemic organ complications and have a mortality rate between 10 and 50% despite improved therapies.

Although mortality rates following major pancreatic surgery have decreased continuously in recent years, they still average 10%, and medical and surgical postoperative complications occur in approximately 40% of patients who undergo major pancreatic surgery. Postoperative complications such as insufficiency of the pancreaticojejunal anastomosis, pancreatic fistula, peripancreatic fluid collection and abscess are chiefly associated with the technical difficulties of performing a proper and safe anastomosis between the pancreatic remnant and the intestine and exocrine pancreatic secretion, which might cause tension on the pancreaticojejunal anastomosis.
All the above clinical conditions can benefit from somatostatin administration. Although its effectiveness in the management of variceal bleeding, pancreatic fistula and prevention of postoperative complications is now clearly established, its use in UGI nonvariceal bleeding and acute pancreatitis is still debated and subjected to continuous investigation. Furthermore, it has become clear that the pharmacological activities and therapeutic efficacy of the native somatostatin and the synthetic analogs are not always identical. Thus, 26 years after the discovery of somatostatin, the understanding of its biology remains a challenge and its therapeutic potential is yet to be fully exploited.

Taking all the above considerations into account, I felt it worthwhile to attempt a critical overview of the recent development in the field. To this end, I have asked a team of international experts to compile comprehensive reviews in order to synthesize the mass of general and specific information existing on the topic. Many of them participated at a symposium which took place in Braine l’Alleud (Belgium), on November 21, 1998, and there they already did a great job. I would like to thank all of them for their contribution despite numerous other calls on their time.

After a review of the clinical pharmacology and safety of somatostatin and analogs, a thoughtful overview of the management strategies in UGI bleeding is presented. The place of this vasoactive peptide in the treatment of variceal and nonvariceal bleeding is then analyzed with the attempt to better define the best drug and regimen. Finally, the management of pancreatic fistula and prevention of complication after major pancreatic surgery with somatostatin or octreotide are thoroughly discussed. The issue is completed by an analysis of pharmacoeconomic issues, whose evaluation is becoming an essential part of any therapeutic guideline.

I would like to thank Mr. Peter Roth and Mrs Andrea Brauns of S. Karger AG for their excellent cooperation during the publication of this supplement. I also acknowledge the help of Miss Gaby Karger in collecting the manuscripts for this issue, nagging authors to submit their papers and interacting with the Editor. Moreover, I am grateful to UCB SA, Pharma Sector, Brussels who supported the symposium and backed the publication costs. Last but not least, my sincere gratitude goes to Dr. Nirjhar Chatterjee and Mrs Catherine Pelissier at the Global Marketing UCB, who rendered this publication possible. They have shown great interest in it from the very beginning and made huge efforts to make this supplement available to the medical community.

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Preface