Can J Anesth/J Can Anesth (2013) 60:492–499
DOI 10.1007/s12630-012-9879-1

REVIEW ARTICLE/BRIEF REVIEW

Mega-dose intravenous octreotide for the treatment of carcinoid crisis: a systematic review

L'octréotide intraveineux en méga-dose pour le traitement d'une crise carcinoïde: une revue méthodique

Nicole Seymour, BSc · Sonja C. Sawh, BScPhm

Received: 10 September 2012 / Accepted: 20 December 2012 / Published online: 18 January 2013

Abstract

Purpose *Carcinoid crises are rare life-threatening events involving cardiac instability when carcinoid tumours release vasoactive peptides. Such events can occur in the perioperative setting. Octreotide, a somatostatin analogue, is administered as a bolus dose of 100-500 μg iv or by infusion to treat carcinoid crises. Due to the apparent low risk-to-benefit profile, a much higher dose is sometimes used in urgent situations. The purpose of this study was to assess the evidence for administering doses or hourly infusions of octreotide that exceeded 1,500 μg iv to treat carcinoid crises. We also sought to identify which patients may require large doses and to describe the adverse effects of such doses.*

Source *We systematically searched Medline, EMBASE, and Cochrane databases and hand-searched reference lists of relevant articles in 2006 and again in 2010 and 2011. All study designs were included in our search. Resolution of crisis symptoms was the primary outcome.*

Principal findings *Eighteen articles were included. No patient died during a carcinoid crisis. A retrospective chart review of 89 patients with carcinoid heart disease reported octreotide doses of 25-54,000 μg to treat carcinoid crises, although neither crisis symptoms nor outcomes were described.*

Conclusion *In the included case reports, carcinoid crises were managed effectively using octreotide 25-500 μg iv. Previous exposure to octreotide and carcinoid heart disease may warrant the need for higher doses. In addition to the low quality of the articles and the small sample size, inconsistent use of the term "\carcinoid crisis" and paucity of reported outcomes were also limitations of this systematic review. These findings highlight the need for further investigation into dose-response relationships of octreotide for the treatment of carcinoid crisis.*

Résumé

Objectif *Les crises carcinoïdes sont des événements rares et potentiellement fatals liés à une instabilité cardiaque causée par la libération de peptides vasoactifs par des tumeurs carcinoïdes. De tels événements peuvent se produire dans le cadre périopératoire. L'octréotide, un analogue de la somatostatine, est administré en bolus de 100-500 μg iv ou en perfusion pour traiter les crises carcinoïdes. En raison du profil risques / bénéfices vraisemblablement bas, une dose bien plus élevée est parfois utilisée dans les situations d'urgence. L'objectif de cette étude était d'évaluer les données probantes décrivant l'administration de doses ou de perfusions horaires d'octréotide excédant 1500 μg iv pour traiter les crises carcinoïdes. Nous avons également tenté d'identifier quels patients pourraient nécessiter de fortes doses et de décrire les effets secondaires défavorables de telles doses.*

This article is accompanied by an editorial. Please see Can J Anesth 2013; 60: this issue.

Author contributions *Nicole Seymour* and *Sonja C. Sawh* helped design the study, conduct the study, analyze the data, and write the manuscript.

S. C. Sawh, BScPhm (✉)
London Health Sciences Centre, 339 Windermere Rd, London, ON N6A 5A5, Canada
e-mail: sonja.sawh@lhsc.on.ca

N. Seymour, BSc
School of Pharmacy, University of Waterloo, 10 Victoria St S, Kitchener, ON N2G 2B2, Canada

N. Seymour, BSc
Pharmacy Department, London Health Sciences Centre, 339 Windermere Rd, London, ON N6A 5A5, Canada

Source *Nous avons mené une recherche méthodique dans les bases de données Medline, EMBASE et Cochrane et avons effectué une recherche manuelle dans les listes de référence des articles pertinents en 2006, puis en 2010 et 2011. Tous les types d'études ont été inclus dans notre recherche. Le critère d'évaluation principal était la résolution des symptômes de crise.*

Constatations principales *Dix-huit articles ont été inclus. Aucun patient n'est décédé pendant une crise carcinoïde. Une révision rétrospective des dossiers de 89 patients présentant une maladie cardiaque carcinoïde a identifié des doses d'octréotide de 25-54 000 µg utilisées pour traiter les crises carcinoïdes, bien qu'il n'y ait aucune description des symptômes de crise ou des pronostics.*

Conclusion *Dans les présentations de cas évaluées, les crises carcinoïdes ont été prises en charge de façon efficace avec des doses d'octréotide de 25-500 µg iv. Une exposition précédente à l'octréotide et une maladie cardiaque carcinoïde pourraient justifier l'utilisation de doses plus élevées. Outre la mauvaise qualité des articles et la petite taille des échantillons, l'usage changeant du terme « crise carcinoïde » et le peu de résultats rapportés ont également limité la portée de cette revue méthodique. Ces résultats soulignent le besoin d'études supplémentaires sur les relations de dose-réponse de l'octréotide pour le traitement des crises carcinoïdes.*

Carcinoid tumours are uncommon, slow-growing, mostly asymptomatic neuroendocrine tumours of enterochromaffin cells.[1] The incidence of carcinoid tumours is estimated to be 3.8-5.2/100,000 people.[1,2] These tumours secrete hormones, including serotonin, bradykinin, histamine, and other vasoactive peptides that are metabolized quickly by the liver after being released into the portal circulation.[3,4] Tumours of the small intestine are most likely to metastasize to the liver, allowing the hormones to escape hepatic metabolism and be released into the systemic circulation.[4,5] These hormones may lead to symptoms such as diarrhea, flushing, tachycardia, and bronchoconstriction, collectively known as carcinoid syndrome.[6] Only 10% of patients with carcinoid tumours will ever experience these symptoms.[7]

When a large number of hormones are released at once, these symptoms become life-threatening and precipitate an event known as a carcinoid crisis.[8] A carcinoid crisis is a medical emergency that involves extreme hypo- or hypertension and sometimes includes flushing, bronchoconstriction, tachycardia, or coma.[6] This is known to happen when patients undergo anesthesia or tumour manipulation, or it may occur spontaneously.[8-10] Serotonin, histamine, bradykinin, kallikrein, and catecholamines are thought to be the main mediators of carcinoid crises.[6] Currently, there are no known indicators to allow clinicians to predict which patients will develop a carcinoid crisis.[11]

Somatostatin is known to inhibit the production of gastric acid, gastrointestinal tract motility, and secretion of bile, colonic fluid, insulin, glucagon, secretin, serotonin, and vasoactive intestinal peptides.[7,12] Octreotide is a somatostatin analogue that acts both to block the release of hormones and to stabilize blood pressure directly.[9] Octreotide administered subcutaneously in doses of 50-1,500 $\mu g \cdot day^{-1}$ is effective for treating symptoms of carcinoid syndrome.[A] For carcinoid crises, octreotide is typically administered in bolus doses or hourly infusion rates of 100-500 µg *iv*.[6,13,14] Due to the apparent low risk-to-benefit profile, much higher doses are sometimes used for patients with complicated conditions in urgent situations. Octreotide is also recommended as a prophylaxis against carcinoid crises when patients with carcinoid tumours undergo surgery.[6] The decisions around the doses of octreotide for prophylaxis and treatment are often left to the anesthesiologist managing the surgical case.

The objective of this study was to assess the state of evidence to inform clinicians on the use of octreotide in doses greater than 1,500 µg *iv* or infusion rates exceeding 1,500 $\mu g \cdot hr^{-1}$ for the treatment of carcinoid crisis. We chose a 1,500 µg dose as the upper limit, as this is the highest recommended dose of octreotide for any of its labelled indications.[A] Furthermore, we attempted to identify risk factors to predict a need for these high doses and examined adverse effects of octreotide in the treatment of carcinoid crisis. In this systematic review, we examined the dose of intravenous octreotide administered for the treatment of carcinoid crisis. This is invaluable information for anesthesiologists and other clinicians who must make incisive critical decisions when presented with this rare life-threatening condition.

Methods

We conducted this systematic review following pre-specified protocols influenced by the guidelines for *Meta-analysis Of Observational Studies in Epidemiology* and *Systematic Reviews of Observational Studies*,[15] and we presented this systematic review in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA* statement.[16] The protocol was determined *a priori* by one of the authors (S.C.S.).

Eligibility criteria

Studies were eligible for inclusion if they included patients who received octreotide intravenously during an episode of

[A] Octreotide (Lexi-Drugs). Lexi-Comp Online™. Hudson, OH: Lexi-Comp Inc [cited June 29, 2011].

suspected or confirmed carcinoid crisis. We sought to compare the outcomes of patients who received an octreotide bolus exceeding 1,500 μg or an infusion at a rate in excess of 1,500 $\mu g \cdot hr^{-1}$ *iv* with outcomes of all patients who received a lower dose of octreotide. Inclusion criteria comprised articles that directly identified a carcinoid crisis as well as articles that described patients with carcinoid tumours who experienced perioperative life-threatening hyper/hypotension for which no other cause could be identified and for which octreotide was used. As no randomized controlled trials were identified, our search criteria were expanded to include non-randomized study designs, such as case reports and case series.

Studies were excluded if there was an inadequate description of the octreotide dose or if octreotide was not administered for the treatment of a crisis. Studies that reported subcutaneous octreotide were also excluded because intravenous octreotide is the current standard of care recommended for carcinoid crisis.[7,17]

Resolution of carcinoid crisis symptoms was the primary outcome. Secondary outcomes included death, length of stay in the intensive care unit (ICU), and total length of stay in hospital.

Search strategy

One reviewer (S.C.S.) systematically searched MEDLINE, Experta Medica (EMBASE), and Cochrane library from the inception of each source until March 2006. A second reviewer (N.S.) updated the search in October 2010 and June 2011 to identify any new articles.

The search strategy was tailored to the functions of each database and included the terms "carcinoid syndrome" or "malignant carcinoid syndrome" AND "octreotide". The MeSH function was used for both terms when searching MEDLINE. The search conducted with EMBASE was limited to articles containing "octreotide" and "carcinoid syndrome" as keywords. The search strategy was developed by a pharmacist with previous experience in systematic reviews (S.C.S.). Carcinoid syndrome was chosen as a broad search term in order to be comprehensive and not to miss any cases that were not directly labelled as crises.

The reference lists of all relevant reviews and included articles were evaluated to identify additional articles meeting our inclusion criteria. All citations were downloaded into RefWorks software.[B]

[B] ProQuest LLC. RefWorks. 2011; Available from URL: http://sfx.scholarsportal.info/western?sid=Refworks%3AWestern%20Libraries&charset=utf-8&__char_set=utf8&genre=article&aulast=ProQuest%20LLC&date=2011&atitle=RefWorks&au=ProQuest%20LLC%20& (accessed November 2012).

Study selection

One reviewer (S.C.S.) evaluated the eligibility of the articles identified in March 2006. The second reviewer (N.S.) evaluated the eligibility of articles identified in March 2006, October 2010, and June 2011. Conflicts were resolved by consensus between both authors.

Data abstraction

Data from the 2006 search were independently abstracted by two reviewers using a pre-specified electronic form. Data from articles identified in subsequent searches were abstracted by a single reviewer (N.S.). Data extracted from each included paper are described in Table 1. Communication was attempted with authors in order to confirm reported values and obtain additional information. When authors of included articles used the terms hypertension, hypotension, bronchoconstriction, and flushing in relation to carcinoid crisis, we considered these as symptoms of carcinoid crisis. Similarly, when authors of included articles described elevated or decreased blood pressure requiring intervention, difficulty breathing, or skin colour abnormalities associated with a carcinoid crisis, these symptoms were considered attributable to carcinoid crisis. We recorded presence of hypertension, hypotension, bronchoconstriction, and flushing when directly stated by the authors to be present and related to carcinoid crisis or when elevated or decreased blood pressure requiring intervention, difficulty breathing, or skin colour abnormalities were stated by the authors as being present and related to carcinoid crisis. We defined resolution of crisis as per the definitions assigned by the authors, and we also accepted any and all adverse events categorized by the authors of the included papers. We collected patient age, sex, tumour location, presence of carcinoid heart disease, prior octreotide use, and carcinoid crisis symptoms in order to evaluate these as possible risk factors for requiring higher doses of octreotide.

Results

Study selection

Our electronic search identified 679 articles, and we identified an additional 15 articles by hand searching relevant articles. After screening titles and abstracts, we retrieved 148 articles for further review. Eighteen publications met inclusion criteria after full-text review. Refer to the Figure for selection of studies.

Table 1 Characteristics of patients, octreotide dose, and carcinoid crisis

Patient characteristics					Octreotide characteristics			Crisis characteristics			
Study	Year	Sex	Age	Carcinoid heart disease?	Used for carcinoid syndrome?	Surgical prophylaxis?	Crisis octreotide dose (*iv*)	Br	F	Hypo	HTN
18	1985	F	53	No	No	No	50 μg × 2	NR	Y	Y	NR
19	1987	F	53	No	No	NR	50 μg × 2	NR	Y	Y	NR
20	1988	M	57	No	No	No	100 μg	Y	Y	Y	NR
21	1991	M	NR	No	NR	No	100 μg	NR	NR	Y	NR
9	1992	F	85	No	NR	NR	25 μg	NR	Y	Y	NR
13	1994	F	53	No	150 μg TID × 1 yr	Yes	200 μg	Y	NR	Y	NR
23	1994	F	79	No	NR	Yes	100 μg	Y	NR	Y	NR
24	1994	F	62	No	No*	No*	5 μg then 95 μg/30 min	NR	Y*	NR	Y
24	1994	M	64	No	No*	Yes*	50 μg/20 min	NR	Y	NR	Y
25	2000	F	50	No	100 μg subcutaneously TID × 3 yr*	Yes	20-50 μg, then 100-200 μg*	N*	N*	Y	NR
26	2000	M	58	Yes	NR	NR	500 μg	Y	Y	Y	NR
27	2003	F	62	Yes	Yes	NR	200 μg	NR	Y	Y	NR
28	2006	M	74	No	LAR 20 mg·month^{-1} intramuscularly	No	50 μg·hr^{-1} × 3 days, reduced dose × 2 days*	NR	Y	NR	NR
29	2007	M	59	No	NR	Yes	100 μg·hr^{-1} × 4 days	NR	Y	Y	NR
33†	2007	F-36 M-53	Mean: 59	Yes	Yes- 30 Unclear- 59	Yes- 87 No- 2	Range: 50-54,000 μg	NR	NR	NR	NR
30	2008	F	56	Yes	1,000 μg·day^{-1}	Yes	100 μg	NR	Y	NR	NR
31	2009	M	84	No	No	NR	50 μg x?	NR	Y	Y	Y
32	2009	M	55	Yes	NR	Yes	100 μg × 3 crises	NR	NR	Y	NR
22	2010	M	80	No	LAR 20 mg·month^{-1} intramuscularly for 1 yr*	No*	50 μg·hr^{-1} × 2 days + 150 μg·hr^{-1} × 8 hr*	NR	Y	Y	NR

Br = bronchoconstriction; F = flushing; H = hypertension; Hypo = hypotension; NR = not reported; LAR = long-acting octreotide brand; TID = three times a day

* Information obtained or confirmed through communication with publication authors

† Except for Weingarten *et al*., each row represents one patient. Data from Weingarten *et al*. are reported as sum, mean, or range as appropriate

Study characteristics

Seventeen of the included articles are case reports involving 18 patients experiencing a carcinoid crisis.[9,13,18-32] One publication is a retrospective chart review describing 89 patients experiencing a carcinoid crisis.[33] Some patients experienced more than one crisis.[25,32] Study characteristics, octreotide dose characteristics, and crisis symptoms of all case reports are shown in Table 1. All studies were published between 1985 and 2010. Seven authors of eight articles kindly provided additional unpublished information.[20-25,28,33]

Octreotide dose and outcomes

Octreotide was effective at treating carcinoid crises at intravenous doses of 25–500 mcg and intravenous infusions at a rate of 50–150 mcg/h in the included case reports that described patient outcomes. Some carcinoid crises were acute and responded fully within one hour of octreotide administration [9,13,18-21,23-27,30-32] while other crises involved persistent hormone secretion requiring an octreotide infusion until symptoms eventually subsided.[22,28,29] Table 2 describes the range of octreotide doses used in the case reports where symptoms resolved within an hour of octreotide administration. One paper describes the use of 50 μg boluses but does not clearly state the number of times these were administered.[31]

Three patients had crises that lasted more than 24 hr.[22,28,29] The infusion doses used for these patients are summarized in Table 3. The first case involved a male patient with an atypical carcinoid tumour of the lung with liver metastases.[28] He had previously received long-acting release (LAR) octreotide 20 mg per month intramuscularly. This patient experienced a carcinoid crisis after administration of his second round of radionuclide therapy. The authors suggested that the 90Y-DOTA-D-Phe(1)-

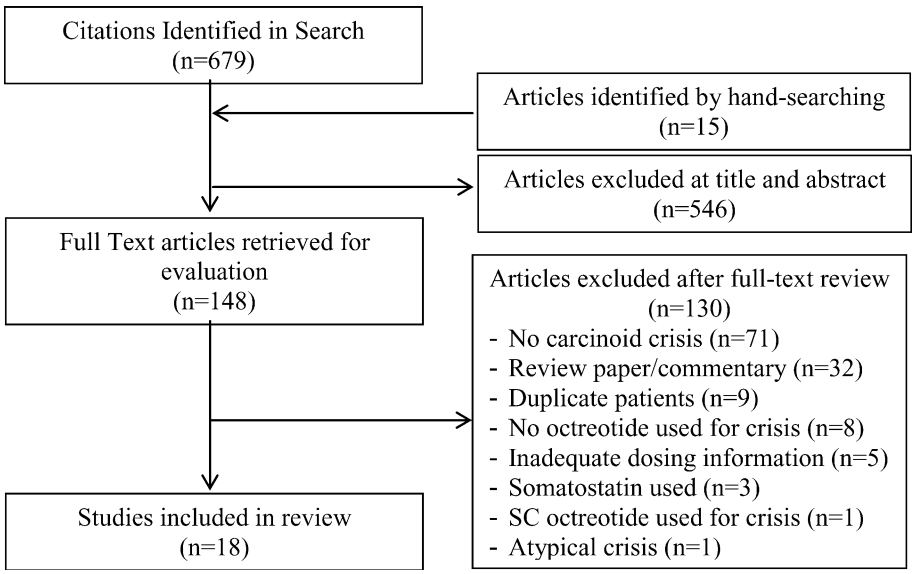

Figure Flow diagram - selection of studies

Tyr(3)-octreotide (90Y-DOTATOC) radionuclide therapy caused this crisis. The patient had one prior and one subsequent uncomplicated radionuclide treatment with a lower exposure to 90Y-DOTATOC. According to personal communications with the author, the infusion of 50 $\mu g \cdot hr^{-1}$ octreotide was performed for three days when the crisis was most severe, and then it was gradually reduced in the next two days as symptoms improved. The patient's length of stay was one week. After one week, the crisis had completely resolved, and during this time, the patient was switched to subcutaneous octreotide in addition to LAR octreotide 30 mg every 28 days. The author also disclosed that this patient had previously experienced a less severe crisis not requiring hospital admission. The second case of prolonged crisis involved an 80-yr-old male patient with a carcinoid tumour of unreported origin and hepatic metastases.[22] This patient experienced a carcinoid crisis that presented as flushing and profound hypotension 24 hr after bland embolization of the main right hepatic lobe.

Table 2 Summary of octreotide bolus doses used in case reports

Total crisis dose (μg)	$n^{\text{Study Ref \#}}$
1-99	2[9,24]
100-199	8[18-21,23,24,30,32]
200-299	2[13,27]
300-399	-
400-499	-
500-599	1[26]

Ranges of bolus doses of octreotide used in case reports resulting in resolution of carcinoid crisis within one hour of octreotide administration

This patient had previous exposure to monthly LAR octreotide 20 mg intramuscularly and received no octreotide as surgical prophylaxis (unpublished information). According to information provided by the author, the patient's crisis was treated with an octreotide infusion at a rate of 50 $\mu g \cdot hr^{-1}$ *iv* for two days, then 150 $\mu g \cdot hr^{-1}$ for eight hours. The third case regarding a prolonged crisis involved a 59-yr-old male with a well-differentiated primary midgut carcinoid tumour with metastases and carcinoid heart disease.[29] The use of LAR octreotide was not reported in this patient who experienced a crisis on the second day after hepatic artery embolization. This patient received octreotide 100 μg prior to the procedure and octreotide 100 $\mu g \cdot hr^{-1}$ *iv* for 24 hr after embolization. Crisis symptoms included flushing, profound hypotension, tachycardia, and dyspnoea. The crisis eventually resolved after treatment with an octreotide infusion at a rate of 100 $\mu g \cdot hr^{-1}$ and oral cyproheptadine for four days along with dobutamine and digoxin to treat acute right ventricular dysfunction (including prolonged symptoms of hypotension) thought to be secondary to carcinoid crisis.

No patient died during crisis, although three patients described in separate case reports died from other complications more than 36 hr post-crisis. The first was a 79-yr-old female with a metastatic carcinoid tumour of the liver. This patient died of bradykinin shock involving intense edema and hypotension 36 hr post-hemicolectomy.[23] An 80-yr-old male with metastatic hepatic carcinoid disease died of hydropneumothorax with complete collapse of the right lung 18 days post-bland embolization of the main right hepatic lobe.[22] Finally, a 57-yr-old male with extensive metastatic carcinoid disease and concomitant psychosis died of respiratory insufficiency

Table 3 Description of octreotide infusion rates used in case reports

Study Ref #	Octreotide infusion rate ($\mu g \cdot hr^{-1}$)	Duration	Total
22	50-150	56 hr	3,600 μg
28	50	5 days	Not reported
29	100	4 days	9,600 μg

Octreotide infusion rates and durations for the three patients in case reports requiring such infusions

and cachexia due to carcinoid tumour progression more than five months after experiencing a carcinoid crisis.[20,21]

Length of stay in hospital and length of stay in the ICU were neither consistently nor uniformly reported, so we were unable to evaluate these outcomes.

Risk factors for higher octreotide doses

Octreotide exposure

Amongst patients described in case reports, those receiving octreotide as maintenance therapy to manage carcinoid syndrome symptoms appeared to receive higher doses of octreotide to manage carcinoid crisis than patients who had no history of octreotide use. In patients who were receiving octreotide maintenance therapy as outpatients, the highest dose of octreotide given to treat a carcinoid crisis was 200 μg. The available data were not comprehensive enough to facilitate quantitative statistical analyses.

One patient experienced seven carcinoid crises during surgery and three carcinoid crises postoperatively. The initial crises responded to octreotide boluses of 20-50 μg, while all later crises slowly responded to and resolved with octreotide boluses of 100-200 μg.[25] This may be an example of tachyphylaxis to octreotide; however, increasing severity of carcinoid crisis could not be ruled out as the need for higher doses.

Carcinoid heart disease

In a retrospective chart review of 100 patients with carcinoid heart disease undergoing surgery, 89 patients were reported to have experienced a carcinoid crisis.[33] According to our communications with the author, a crisis was defined by the investigator as the need for octreotide administration intraoperatively. In many cases, reported changes in blood pressure did not appear to be life-threatening; therefore, we are uncertain whether these patients were actually experiencing a carcinoid crisis (unpublished data). The median octreotide dose was 1,500 μg, although no description of carcinoid crisis symptoms or resolution was available (unpublished data). Carcinoid heart disease may be an independent predictor of complications during surgery and may also signal the need for higher doses of octreotide to treat a crisis.[33]

Consequences of octreotide in the treatment of carcinoid crisis

Adverse effects were not well reported in any study. No outcomes were reported for those patients receiving octreotide doses greater than 1,500 μg *iv*.

Discussion

Octreotide doses ranging from 25-500 μg *iv* and infusions at rates of 50-150 $\mu g \cdot hr^{-1}$ *iv* were effective for reversing carcinoid crises. Patients with prior exposure to octreotide for the management of carcinoid syndrome received slightly higher doses of octreotide to manage crises than those patients who had no history of octreotide use. During perioperative assessment, anesthesiologists may find that a patient's previous use of octreotide is a predictive tool to estimate the dose of octreotide necessary to treat potential intraoperative carcinoid crises. This is corroborated by two studies in which the use of higher doses of octreotide to manage carcinoid syndrome was correlated with the need for higher octreotide doses to manage intraoperative carcinoid symptoms.[30,33] Due to limited evidence, we cannot make causal statements regarding octreotide and the development of tachyphylaxis. Tachyphylaxis has been shown to develop after months or years of treatment in nearly all patients and is initially overcome by increasing the dose of octreotide.[34] A decreased response to octreotide may involve down-regulation of receptors and/or various types of resistance to octreotide, including gene mutations.[35] In our review, one patient experiencing seven carcinoid crises required increasing doses of octreotide with each subsequent crisis.[25]

Carcinoid heart disease is typically a late manifestation of carcinoid tumours, and patients with carcinoid heart disease may have an increased risk of perioperative complications.[14,36] This was supported in a study by Weingarten *et al* where a high proportion of patients with carcinoid heart disease were reported to have experienced a carcinoid crisis.[33] This study also presents the possibility that patients with carcinoid heart disease may require higher doses of octreotide should a crisis occur.[33]

Side effects of subcutaneous octreotide therapy are minimal and can include fat malabsorption, pain at the injection site, rash, nausea and vomiting, abdominal discomfort, dizziness, cholestasis, and headache.[37] Octreotide is also known to cause hyperglycemia through suppression of insulin.[30,38] In a case series, octreotide-induced

hyperglycemia has been shown whereby patients receiving higher doses of octreotide for surgical prophylaxis experienced elevated blood glucose and required insulin administration.[30] Somatostatin inhibits many other hormones, including growth hormone and thyroid stimulating hormone.[39] Since octreotide is a somatostatin analogue, inhibition of these same hormones could lead to adverse effects. Furthermore, since octreotide can be immediately effective for reversing life-threatening carcinoid crises, side effects are likely to go unnoticed or are imperceptible compared with the trauma of the crisis and surgery themselves.

Each tumour secretes a unique cocktail of hormones, which makes each carcinoid crisis different and leads to discrepancy regarding the definition, symptoms, and treatment of carcinoid crisis. In addition, the unpredictability and urgency of carcinoid crisis makes it very difficult to research the underlying process. There is still much to learn about the physiology of carcinoid tumours, carcinoid crises, and the mechanism of octreotide in the treatment of carcinoid crisis. Understanding risk factors could be valuable to anesthesiologists in the prophylactic management (i.e., perioperative) and incidental treatment (i.e., intraoperative) of carcinoid crisis.

This systematic review included extensive searches across multiple databases and incorporated best available evidence for the clinical question.[16] The heterogeneity in the definition of carcinoid crisis, the incomplete reporting of outcomes of interest, and the small sample size limit the ability to make causal inferences. The objective of this review was to assess the state of the evidence to support the use of octreotide boluses or hourly infusion rates in doses greater than 1,500 μg *iv* for the management of carcinoid crisis. The results of the review clearly show the lack of evidence on this important clinical question. Nevertheless, the paucity of reported safety concerns may encourage clinicians to utilize higher doses of octreotide when efficacy is the major concern in the presence of this life-threatening event. More research is needed before we can support or refute the necessity, side effects, and outcomes of octreotide doses greater than 1,500 μg *iv* and infusion rates in excess of 1,500 $\mu g \cdot hr^{-1}$. In particular, guidelines should be established to identify which patients, if any, may benefit from such large doses. In light of the urgent and unpredictable nature of carcinoid crisis, the information presented should provide anesthesiologists and other clinicians with guidance to make the proper preoperative preparations for patients at risk.

Acknowledgements We are extremely grateful to the many authors who provided additional data for their included articles. In particular, we sincerely thank Dr. Toby Weingarten for his significant contributions towards the interpretation of his study.

Funding The evidence synthesis on which this article was based was not funded. Support for the authors was provided by their employer, the Pharmacy Department, London Health Sciences Centre, London, Ontario, Canada.

Role of funding source The funder played no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication. They accept no responsibility for the contents.

Competing interests None declared.

References

1. *Yao JC*, *Hassan M*, *Phan A*, *et al*. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-72.
2. *Maggard MA*, *O'Connell JB*, *Ko CY*. Updated population-based review of carcinoid tumors. Ann Surg 2004; 240: 117-22.
3. *Modlin IM*, *Oberg K*, *Chung DC*, *et al*. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008; 9: 61-72.
4. *Veall GR*, *Peacock JE*, *Bax ND*, *Reilly CS*. Review of the anaesthetic management of 21 patients undergoing laparotomy for carcinoid syndrome. Br J Anaesth 1994; 72: 335-41.
5. *Grahame-Smith DG*. The carcinoid syndrome. Am J Cardiol 1968; 21: 376-87.
6. *Kvols LK*. Therapeutic considerations for the malignant carcinoid syndrome. Acta Oncol 1989; 28: 433-8.
7. *van der Lely AJ*, *de Herder WW*. Carcinoid syndrome: diagnosis and medical management. Arq Bras Endocrinol Metabol 2005; 49: 850-60.
8. *Kahil ME*, *Brown H*, *Fred HL*. The carcinoid crisis. Arch Intern Med 1964; 114: 26-8.
9. *Comunale ME*, *Neilly SA*. Use of somatostatin analog in the treatment of hypotension during bowel surgery. J Cardiothorac Vasc Anesth 1992; 6: 606-8.
10. *Jahng AW*, *Liao SS*. Successful palliation with octreotide of a neuroendocrine syndrome from malignant melanoma. J Pain Symptom Manage 2006; 32: 191-5.
11. *Orbach-Zinger S*, *Lombroso R*, *Eidelman LA*. Uneventful spinal anesthesia for a patient with carcinoid syndrome managed with long-acting octreotide. Can J Anesth 2002; 49: 678-81.
12. *Lamberts SW*, *Krenning EP*, *Klijn JG*, *Reubi JC*. The clinical use of somatostatin analogues in the treatment of cancer. Baillieres Clin Endocrinol Metab 1990; 4: 29-49.
13. *Quinlivan JK*, *Roberts WA*. Intraoperative octreotide for refractory carcinoid-induced bronchospasm. Anesth Analg 1994; 78: 400-2.
14. *Mancuso K*, *Kaye AD*, *Boudreaux JP*, *et al*. Carcinoid syndrome and perioperative anesthetic considerations. J Clin Anesth 2011; 23: 329-41.
15. *Stroup DF*, *Berlin JA*, *Morton SC*, *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12.
16. *Moher D*, *Liberati A*, *Tetzlaff J*, *PRISMA Group*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
17. *Goldfinger SE, Strosberg JR*. Treatment of the carcinoid syndrome. Waltham, MA: UpToDate; 2011. Available from URL: http://www.uptodate.com/contents/treatment-of-the-carcinoid-syndrome?source=search_result&search=carcinoid+syndrome+adult&se (accessed November 2012).

18. *Kvols LK*, *Martin JK*, *Marsh HM*, *Moertel CG*. Rapid reversal of carcinoid crisis with a somatostatin analogue. N Engl J Med 1985; 313: 1229-30.
19. *Marsh HM*, *Martin JK Jr*, *Kvols LK*, *et al*. Carcinoid crisis during anesthesia: successful treatment with a somatostatin analogue. Anesthesiology 1987; 66: 89-91.
20. *Ahlman H*, *Ahlund L*, *Dahlstrom A*, *Martner J*, *Stenqvist O*, *Tylen U*. SMS 201-995 and provocation tests in preparation of patients with carcinoids for surgery or hepatic arterial embolization. Anesth Analg 1988; 67: 1142-8.
21. *Ahlman H*, *Wangberg B*, *Jansson S*, *et al*. Management of disseminated midgut carcinoid tumours. Digestion 1991; 49: 78-96.
22. *Fujie S*, *Zhou W*, *Fann P*, *Yen Y*. Carcinoid crisis 24 hours after bland embolization: a case report. Biosci Trends 2010; 4: 143-4.
23. *Sarantopoulos C*, *Fassoulaki A*, *Alexandris A*. Anesthetic management of two patients undergoing laparotomy & hepatectomy for carcinoid syndrome. Acta Anaesthesiol Belg 1994; 45: 83-7.
24. *Warner RR*, *Mani S*, *Profeta J*, *Grunstein E*. Octreotide treatment of carcinoid hypertensive crisis. Mt Sinai J Med 1994; 61: 349-55.
25. *Cortinez F LI.* Refractory hypotension during carcinoid resection surgery. Anaesthesia 2000; 55: 505-6.
26. *Janssen M*, *Salm EF*, *Breburda CS*, *et al*. Carcinoid crisis during transesophageal echocardiography. Intensive Care Med 2000; 26: 254.
27. *Kharrat HA*, *Taubin H*. Carcinoid crisis induced by external manipulation of liver metastasis. J Clin Gastroenterol 2003; 36: 87-8.
28. *Davi MV*, *Bodei L*, *Francia G*, *et al*. Carcinoid crisis induced by receptor radionuclide therapy with 90Y-DOTATOC in a case of liver metastases from bronchial neuroendocrine tumor (atypical carcinoid). J Endocrinol Invest 2006; 29: 563-7.
29. *Majeed F*, *Porter TR*, *Tarantolo S*, *Duhachek-Stapelman A*, *Xie F*, *Elhendy A*. Carcinoid crisis and reversible right ventricular dysfunction after embolization in untreated carcinoid syndrome. Eur J Echocardiogr 2007; 8: 386-9.
30. *Castillo JG*, *Filsoufi F*, *Adams DH*, *Raikhelkar J*, *Zaku B*, *Fischer GW*. Management of patients undergoing multivalvular surgery for carcinoid heart disease: the role of the anaesthetist. Br J Anaesth 2008; 101: 618-26.
31. *Sinha V*, *Dyer P*, *Roy-Choudhury S*, *Geh JI*, *Karandikar S*. Case of carcinoid crisis following a fine-needle biopsy of hepatic metastasis. Eur J Gastroenterol Hepatol 2009; 21: 101-3.
32. *Yazbek-Karam VG*, *Haswani RW*, *Mousallem NM*, *et al*. Severe intra-operative carcinoid crisis in a patient having carcinoid heart disease. Acta Anaesthesiol Scand 2009; 53: 414-5.
33. *Weingarten TN*, *Abel MD*, *Connolly HM*, *Schroeder DR*, *Schaff HV*. Intraoperative management of patients with carcinoid heart disease having valvular surgery: a review of one hundred consecutive cases. Anesth Analg 2007; 105: 1192-9.
34. *Plockinger U*, *Wiedenmann B*. Neuroendocrine tumors. Biotherapy. Best Pract Res Clin Endocrinol Metab 2007; 21: 145-62.
35. *Hofland LJ*, *Lamberts SW*. The pathophysiological consequences of somatostatin receptor internalization and resistance. Endocr Rev 2003; 24: 28-47.
36. *Kinney MA*, *Warner ME*, *Nagorney DM*, *et al*. Perianaesthetic risks and outcomes of abdominal surgery for metastatic carcinoid tumours. Br J Anaesth 2001; 87: 447-52.
37. *Deguchi H*, *Deguchi K*, *Tsukada T*, *et al*. Long-term survival in a patient with malignant carcinoid treated with high-dose octreotide. Intern Med 1994; 33: 100-2.
38. *Sullivan SJ*, *Schonbrunn A*. Characterization of somatostatin receptors which mediate inhibition of insulin secretion in RINm5F insulinoma cells. Endocrinology 1987; 121: 544-52.
39. *Guillemin R*, *Gerich JE*. Somatostatin: physiological and clinical significance. Annu Rev Med 1976; 27: 379-88.