Diagnostic and treatment modalities in carcinoid tumours

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Chapter 5.1

Long-term palliation in metastatic carcinoid tumours with various applications of meta-iodobenzylguanidine (MIBG):
pharmacological MIBG, $^{131}$I-labelled MIBG and the combination

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Abstract

Carcinoid tumours are rare, but well known for their characteristic presentation with diarrhoea and flushes due to overproduction of serotonin in the case of liver metastases. Treatment is mainly based on the reduction of vasoactive peptide hypersecretion and symptomatic improvement. Octreotide and interferon are widely applied and effective treatment options to induce symptomatic improvement and, to a lesser extent, biochemical response. The main drawbacks, however, are the need for frequent injections and/or the occurrence of side effects.

A rather new approach is the application of meta-iodobenzylguanidine (MIBG), which resembles noradrenalin and serotonin. In carcinoid patients, MIBG is taken up in the tumour cells and stored in the neurosecretory granules. When labelled with $^{131}$iodine, radionuclide imaging is positive in up to 70% of the patients. In these patients, two cycles of a therapeutic dose of radioactive MIBG may induce long-lasting palliation (8 months) by internal irradiation. Also, the non-radioactive MIBG compound may be effective in palliation, even in patients with a negative scan. The mode of action is based on specific tumour acidification as found in animal models, and/or based on its effect as a false neurotransmitter.

Three case reports demonstrate different therapeutic possibilities of MIBG: 1) symptomatic relief with unlabelled MIBG, which is a safe and simple treatment; 2) the long-term palliation following radioactive treatment; and 3) an additional new aspect of predosing with unlabelled MIBG followed by radioactive MIBG led to improved tumour targeting and impressive clinical response.
Long-term palliation with various applications of MIBG

Introduction

Carcinoid tumours are neuroendocrine tumours, mostly derived from the midgut. They often present with extensive liver metastases leading to the characteristic attacks of diarrhoea and flushes: the carcinoid syndrome. Elevated urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), the degradation product of serotonin, is characteristic. Treatment of metastatic carcinoid is aiming at symptomatic improvement and reduction of hormonal hypersecretion. Well-known treatment options (Table 1) are octreotide and interferon-α. Symptomatic improvement can be achieved in 60-80% of patients and biochemical response in 30-40%, but tumour reduction is only occasionally described. The need for repeated injections, for octreotide two or three times per day, and for interferon three times a week, is a clear disadvantage.

A novel approach is the application of meta-iodobenzylguanidine (MIBG), a biogenic amine precursor, which resembles noradrenaline and serotonin. Initially, MIBG has been developed as a derivate of the neuroblocking agents bretylium and guanethidin. Due to its high affinity for the noradrenaline transporter protein, it is taken up by chromaffin cells and stored in neurosecretory granules. Based on this mechanism of retention, radionuclide diagnostic imaging with a tracer dose of (1 mCi=37 mBq) $^{131}$I-MIBG was introduced in 1984 when the first report of a positive scan at carcinoid tumour deposits appeared. Currently, a positive MIBG scan is present in up to 70% of carcinoid patients. Apart from its help in tumour imaging, $^{131}$I-MIBG has been applied in a much higher dose (200 mCi=7.4 GBq) in cases with a positive scan to provide a selective local effect by internal irradiation. Two cycles with an interval of 6 weeks resulted in a significant symptomatic response for 8 months in 60% of 30 patients with metastatic carcinoid, despite frequent (47%) pre-treatment with octreotide or interferon. The main disadvantage is the need for isolation according to legislation; otherwise, side effects were mild and rapidly reversible.

In addition to the radiotherapeutic effects of $^{131}$I-MIBG, the unlabelled compound has demonstrated several biological and pharmacological effects in tumour cell lines (e.g. L1210 leukaemia, N1E115 neuroblastoma) and animal models (RIF-1 tumour bearing mice). The cytotoxic effect of MIBG is related with inhibition of mitochondrial respiration and is dependent on anaerobic glycolysis, resulting in enhanced glucose consumption, increased lactic acid production, inhibition of oxygen consumption and decreased adenosine triphosphate levels. This tumour-specific effect might also enhance the result of cytostatic drugs, as has been described for alkylating agents such as melphalan, mitomycin C and cisplatinum. Encouraged by these findings, we also applied the non-radioactive or unlabelled MIBG in pharmacological doses of 10-40 mg/m². For comparison, the $^{131}$I-labelled compound contains only 5 mg MIBG. Treatment with the unlabelled MIBG proved to be safe and simple: three courses at 4-weeks intervals with a 4-hour infusion of increasing doses of MIBG resulted in a significant symptomatic
response in 60% of 20 patients during 4-5 months. Side effects were mild and of short duration: in 6/20 patients, some changes in blood pressure (hypertension in four and hypotension in two) were encountered during infusion, which resolved within 20-30 minutes. In only one of these six patients, a single dose of an antihypertensive drug was needed. The unlabelled component was studied in patients with a negative scan or in poor condition.\(^5\)

A third possibility to apply MIBG is provided by the combination of the radioactive (‘hot’) with the unlabelled (‘cold’) MIBG. In a pilot study of 10 patients with a negative MIBG scan, predosing with unlabelled MIBG lead to improved tumour targeting of the radiolabelled MIBG and hence a positive scan.\(^8\) In five of these 10 patients, uptake and retention in tumour deposits improved significantly. The combined treatment consisting of two cycles, with 6-week interval, of a 4-hour infusion of unlabelled MIBG (20 mg/m\(^2\)) immediately followed by a 4-hour infusion of 200 mCi \(^{131}\)I-MIBG resulted in long-lasting palliation in four out of 5 patients with some biochemical responses.

To demonstrate the spectrum of diagnostic and therapeutic options in patients with metastatic carcinoid and to illustrate the potentially long-lasting response to MIBG therapy, we report three case histories.
Table 1. Palliative treatment in metastatic carcinoid

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<th>Treatment</th>
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<th>Author</th>
<th>Ref nr.</th>
<th>Yr</th>
<th>Number patients</th>
<th>Subjective response %</th>
<th>Duration of response (months)</th>
<th>Biochemical response %</th>
<th>Tumour response</th>
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<td>3x500-1000 µg</td>
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<td>31</td>
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<td>6</td>
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<td>Safe and simple</td>
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*n.m.= not mentioned
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Patients

Patient A

A woman born in 1951 presented with abdominal pain and a palpable mass in the lower abdomen in August 1992. A diagnosis of ovarian cancer was not confirmed at laparoscopy, but malignant ascites and liver metastases were present. Unexpectedly, a liver biopsy showed carcinoid tumour. In retrospect, she suffered from flushes which she related to pending meno-
pause despite her young age (41 years), and some diarrhoea for the previous month. The
diagnosis of metastatic carcinoid was confirmed by a strongly elevated urinary 5-HIAA
excretion (688 μmol/24h; normal < 40). Biochemical liver tests were within normal range
despite extensive lesions at computed tomography (CT) scan (Figure 1A,B). Subsequently,
she was referred to our hospital. An $^{111}$I-MIBG scan showed retention in the left liver lobe
(Figure 1C). $^{111}$In-pentetreotide scintigraphy was also positive (Figure 1D). As symptoms
were mild, she was treated with unlabelled MIBG according to a phase II trial including three
cycles of escalating doses (10, 20 and 40 mg/m² in a 4-hour infusion at 4-week intervals).
MIBG.1/2 H₂SO₄ was synthesized from the hydrochloride salt of meta-iodobenzylamine by a
modified method of Wieland as described earlier¹, and originated from EMKA Chemie
(Neufahrn, Germany).

At the end of the 4-hour infusion of MIBG, the blood pressure rose from 110/65 to 170/105
mmHg, accompanied by a feeling of weakness and flushes, which recovered spontaneously
within 30 min. For the second MIBG cycle after 4 weeks, precaution was taken with a 50%
dose reduction and premedication of octreotide (1x 200 mcg s.c.). This time, side effects did
not occur. One week later, diarrhoea and flushes disappeared completely and she felt well
during the following 11 months, with no need for additional treatment. The urinary 5-HIAA
excretion was stable.

In August 1993, she developed acute abdominal pain due to gastric perforation of a benign
gastric ulcer, which was oversewn. The primary carcinoid tumour, which was undetected
so far, was present in the ileum and caused some obstruction: therefore, an ileo-ileostomy
was performed. The liver metastases as well as peritoneal deposits were unchanged
compared with the findings at laparoscopy one year earlier.

After an uneventful recovery, she was well for several months, when her condition
deteriorated in 6-8 weeks. She suffered from lack of appetite and some diarrhoea, but not
the classical features of carcinoid crisis; also oedema, ascites and hypoalbuminaemia
developed. To induce a long-lasting response and based on our previous promising results
in patients with a positive MIBG-scan to radioactive $^{111}$I-MIBG, she received 200 mCi by
a 4-hour infusion. The subsequent improvement was striking: restoration of her condition
with disappearance of oedema and she could regain an almost normal life. Urinary 5-
HIAA excretion dropped from 973 to 221 μmol/24h. She remained well for another 8
months without additional medication.
In November 1994, she then developed malignant ascites and heart failure based on a tricuspid regurgitation. In the absence of diarrhoea and flushes, interferon-α was preferred, because this may induce tumour regression more often than octreotide. Interferon-α (thrice weekly 6 mU s.c.) induced reduction of 5-HIAA excretion (from 1620 to 1063) but, finally, all attempts failed and she died in June 1995 almost 3 years after the initial diagnosis of metastatic carcinoid.

In summary, this woman responded well during 2 years with a relatively simple administration of MIBG, in either pharmacological doses or the radioactive compound.

**Figure 1.** Two sections of the CT-scan (A & B) show multiple liver metastases in patient A with a carcinoid syndrome and elevated 5-HIAA urinary excretion. The $^{131}$I-MIBG scintigraphy (C) shows retention in the large liver metastasis in the left lobe. The octreotide scintigraphy (D) reveals a hot spot in the left liver lobe, but also normal activity in the kidneys. In addition, two mid-abdominal spots interpreted as lymph node metastases.
Patient B

A woman born in 1930 presented with diarrhoea and abdominal pain in 1978. Based on a small bowel radiography, a diagnosis of Crohn’s disease of the terminal ileum was made. When, in 1981, symptoms increased, a small bowel resection was performed. However, at pathology, no signs of Crohn’s disease were present, but a carcinoid tumour with mesenteric lymph node metastases was found. She was well until 10 years later (1991), when she again developed abdominal pain, this time accompanied by flushes and fever: liver metastases and stenosis of the small bowel anastomosis were found. She was admitted to our hospital. Radionuclide imaging showed only minimal retention of $^{131}$I-MIBG in the tumour deposits. After a right hemicolecction in May 1991, abdominal symptoms rapidly decreased. Resection of the liver metastases was technically not feasible; in addition, micro tumour deposits at the peritoneum were present, but without ascites.

In December 1992, flushes were mild, but accompanied by severe left-sided headaches and mild sinus tachycardia. Three cycles of unlabelled MIBG according to the aforementioned phase II trial of escalating doses of 10, 20 and 40 mg/m$^2$ by a 4-hour intravenous infusion at 4-week intervals, resulted in a clear improvement of symptoms and stabilisation of 5-HIAA excretion (from 393 to 334 µmol/24h) at the cost of no side effects. One year later when symptoms reappeared, two more cycles resulted in a similar subjective improvement and 5-HIAA excretion dropped from 1012 till 787 µmol/24h. Two years later in 1995, her condition deteriorated gradually: diarrhoea as well as fever and malaise, accompanied by a high 5-HIAA urinary excretion (2410 µmol/24h). Initially, the $^{131}$I-MIBG scan was negative, but following a pharmacological dose of MIBG, improved tumour targeting resulted in a positive scan (Figure 2A,B). Based on the clear retention in the liver metastases, she received a therapeutic dose of radioactive MIBG (200 mCi) after predosing with pharmacological MIBG. For this treatment, isolation for 5 days is necessary according to legislation, but side effects did not occur. Two cycles with a 6-week interval resulted in an excellent response (Figure 2C,D) both in symptoms and biochemistry (5-HIAA excretion dropped from 2410 to 614 µmol/24h) which lasted 10 months. When diarrhoea and flushed recurred, daily octreotide injections (3 x 100 mcg) were started with subjective improvement, and a decrease of 5-HIAA excretion from 1050 to 710 µmol/24h occurred. Although symptoms of the carcinoid syndrome itself were minimal, her general condition gradually deteriorated and signs of heart failure developed. Fibrosis of the tricuspid valve, already present at some degree in 1994, had increased dramatically in 1996. Eventually, she died in September 1997, 16 years after the initial diagnosis and 6 years from the detection of liver metastases, during which the quality of life was excellent with occasional application of MIBG.

In conclusion, the atypical symptoms of fever and headache, as well as the characteristic flushes and diarrhoea, responded equally well to MIBG in pharmacological doses and to a
radioactive treatment; with this simple and safe treatment no additional treatment was needed for 3 years.

**Figure 2.** The $^{131}$I-MIBG scintigraphy in patient B showing only minimal retention (A) in the liver metastases, but clearly improved tumour targeting (B) following pre-treatment with unlabelled MIBG, revealing at least three 'hot' areas. At the CT-scan before (C) and after (D) the combined treatment with radioactive and unlabelled MIBG, central necrosis appears as a sign of response.
Patient C

A young woman born in 1957 presented in January 1995 with a 6-month history of diarrhoea, weight loss (4 kg) and flushes. At physical examination, an enlarged liver, a cardiac murmur and a painful subcutaneous nodule in the buttock were found. A clinical diagnosis of carcinoid syndrome was confirmed by histology and an elevated urinary 5-HIAA excretion (1665 μmol/24h). CT-scan showed extensive liver metastases (Figure 3A). In addition, ultrasound of the heart revealed some fibrosis of the tricuspid valve. A diagnostic 131I-MIBG scan as well as the octreotide scintigraphy were positive.

She was then treated with the unlabelled MIBG according to the aforementioned phase II study: a total of three cycles of increasing doses (10, 20 and 40 mg/m²) at 4-week intervals resulted in clear improvement: fewer flushes and only occasionally diarrhoea, with the need for less loperamide medication. Also, some decrease in 5-HIAA excretion was present (from 1665 to 1495 μmol/24h). She was well for 4 months.

New symptoms arose due to skeletal metastases in the spine at C5, Th8, L1 and L3. Based on 131I-MIBG imaging revealing improved tumour targeting by pre-treatment with unlabelled MIBG (Figure 3B), she was treated with the combination of 131I-labelled and unlabelled MIBG in May and August 1995. Symptoms of pain improved and 5-HIAA excretion decreased further to 1000 μmol/24h. This response lasted for 5 months without additional treatment.

In January 1996 diarrhoea and flushes recurred, with only minimal increase in 5-HIAA excretion. Symptoms resulted well to daily injections with octreotide (3 x 100 mcg s.c.): diarrhoea improved significantly, flushes remained unchanged, and 5-HIAA excretion dropped from 1178 to 670 μmol/24h.

At the end of 1997, symptoms recurred and the 5-HIAA excretion increased; based on the earlier favourable effect, the patient strongly preferred a repeated radioactive treatment with MIBG, but she felt too weak for the required isolation of 5 days. The octreotide treatment was then doubled in dose. Nevertheless, her condition deteriorated: two epileptic attacks and other neurological symptoms occurred, due to malignant meningitis, which was irradiated.

However, her neurological condition deteriorated and she died in February 1998, 3 years after the initial diagnosis.

In summary, in this young woman MIBG treatment resulted in a subjective and biochemical response for almost 1 year. Although treatment with octreotide was equally effective, she preferred MIBG, when she suffered disease progression while on octreotide therapy.
Figure 3. CT-scan of the liver in patient C revealed extensive carcinoid metastases with enlargement of the left lobe (A).
The corresponding $^{131}$I-MIBG scintigraphy (B) showed some retention initially, but significantly more so after premedication with unlabelled MIBG. In the middle, the findings during the combined treatment

A

B

Discussion

The diagnosis of metastatic carcinoid may be difficult as illustrated by the case reports. In patient A, symptoms were mild and not clearly mentioned at presentation; in patient B, initial diagnosis was Crohn’s disease. Only in patient C were symptoms clearly those of carcinoid syndrome. To confirm the diagnosis of metastatic carcinoid, urinary 5-HIAA excretion is pathognomonic.\(^3\)

Two tumour-seeking imaging techniques to detect tumour deposits are of value for staging, but especially for treatment selection, as a positive test predicts clinical response: MIBG and octreotide scintigraphy.\(^4\) MIBG can be transported over the cell membrane mainly by an active uptake mechanism and to a lesser extent through diffusion. In the tumour cell, it is stored in the neuroendocrine granules. When labelled with radioactive iodine, tumour deposits can be detected by total body imaging.

In comparison with the high sensitivity (\(>90\%\)) and specificity (close to 100\%) of MIBG scintigraphy in phaeochromocytoma and neuroblastoma, the cumulative sensitivity of $^{131}$I-MIBG imaging in carcinoid is lower (70\%). Liver metastases are most frequently and best detected. Because of the normal MIBG uptake in the liver, delayed imaging using the $^{131}$iodine rather than the $^{123}$iodine label is preferable; furthermore, single photon emission tomography is preferred. Although pathological scintigrams most often occur in association with (but also in the absence of) the carcinoid syndrome, no correlation
between the scintigraphic results and the urinary excretion of 5-HIAA is found. Many drugs are known or may be expected to interfere with the uptake and/or retention of $^{131}$I-MIBG in neurocrest tumours. This may be the cause of a false negative scan. Patients should be taken off these drugs prior to MIBG scintigraphy whenever possible.

Octreotide (an analogue of somatostatin) scintigraphy is based on a totally different mechanism: the somatostatin analogue, octreotide, labelled with $^{111}$-indium ($^{111}$In-pentetreotide) binds to the somatostatin receptor on the surface of the tumour cell.

Cumulative results of $^{111}$In-pentetreotide show a high affinity to carcinoid tumours (86%). Several factors may interfere with the binding of $^{111}$In-pentetreotide to the receptor: increased production of somatostatin by the tumour leading to saturation of the receptors, different subtypes of somatostatin receptors showing different affinity, and expression of receptor varying with the degree of differentiation of the tumour. Although it has been advocated to refrain from somatostatin therapy prior to scintigraphy in order not to saturate the receptors, and ultimately to avoid a false negative scan, the opposite of increased contrast of liver metastases during therapy has also been described. Various other tumours, however, are also positive, thereby limiting the specificity of a positive scintigram.

The experience with a combination of the two techniques is limited, but our own observations in a group of 20 patients revealed a sensitivity of 95% using the combination of both techniques.9 A French study in 31 patients confirmed these findings.10 In patient A, tumour sites were detected by $^{131}$I-MIBG as well as $^{111}$In-pentetreotide scintigraphy, but $^{111}$In-pentetreotide scintigraphy detected two mid-abdominal sites that were negative with the $^{131}$I-MIBG scan and were interpreted as lymph node metastases rather than the primary tumour. Almost 1 year after the diagnosis, the primary tumour was found in the distal ileum by coincidence during laparotomy because of a perforated benign gastric ulcer.

As the carcinoid syndrome is usually due to diffuse liver metastases, curative or palliative surgical resection is often not possible. The main goal of treatment is palliative: improvement of symptoms and quality of life. When the $^{131}$I-MIBG scintigraphy (1 mCi=37 mBq) shows significant tumour uptake, treatment with a higher dose (200 mCi=7.4 GBq) $^{131}$I-MIBG may offer long-lasting symptomatic relief in 60% of patients. In case the $^{131}$I-MIBG scan shows faint tumour uptake, unlabelled MIBG might still be effective. A pharmacological dose of 10-40 mg/m$^2$ (compared with 1 mg for the diagnostic imaging dose and 5 mg for the $^{131}$I-MIBG treatment dose) may alleviate symptoms. As aforementioned, the presumed mode of action is specific tumour acidification or providing a false neurotransmitter. The radiolabelled MIBG acts as an internal radiation source. The median duration of response with $^{131}$I-MIBG is much longer, 8 months compared to 4.5 months with unlabelled MIBG. In general, MIBG treatment is well tolerated. The main disadvantage of radioactive labelled MIBG is the need for isolation of the patient based on legislation, while unlabelled MIBG is safe and simple with only minor, short-lasting changes in blood pressure.5 In our patients, both the $^{131}$I-MIBG and
the $^{111}$In-pentetreotide scintigraphy were positive. Patient A experienced an excellent response to radioactive MIBG. Patient B repeatedly responded very well to the simple infusion of unlabelled MIBG. Later on, a rather new approach was applied in patients A and C: unlabelled MIBG immediately followed by infusion of radioactive MIBG. This predosing technique resulted in an improved tumour targeting: more retention in tumour deposits and less in the normal tissues. Preliminary data showed improvement of tumour/non-tumour ratio of the radiopharmacon in 5/10 patients, making radioactive treatment a possibility in five cases, and resulted in long-lasting response in four of them. Subsequently, in an extended series, improved targeting was present in 17/24 patients.

At present, the somatostatin analogue octreotide is considered by many physicians to be the first choice of treatment. A positive $^{111}$In-pentetreotide scintigram may be indicative for a clinical response to treatment with somatostatin analogues. Octreotide can induce symptomatic improvement in about 80% of patients, although a good clinical response is not always reflected by a reduction of 5-HIAA excretion in urine, as biochemical response is present in 70%.$^{12-14}$ A major disadvantage is the need for subcutaneous injections twice (or sometimes thrice) daily. This drawback may be overcome by new slow-release preparations (one intramuscular injection per 2-4 weeks).$^{15}$ Our patients were reluctant to start this treatment, as they presented with only mild symptoms. Therefore, we treated them with the unlabelled MIBG. During follow-up, octreotide was initiated in patient B and C, resulting in symptomatic improvement and some decrease of 5-HIAA excretion. Nowadays, wide experience$^{15-18}$ with interferon is also promising as a palliative treatment as reported by the Scandinavian group,$^2$ but despite a biochemical response in our patients B and C, a symptomatic effect was not seen.

Although metastatic carcinoid is a slowly growing malignancy, the concomitant symptoms of hormone production can make it a complicated disease. After an era of monotherapy, combination therapy has now been tested, e.g. interferon plus octreotide$^{19}$ or combinations with chemotherapy.$^{20-23}$ Currently, the combination of interferon and MIBG is under investigation.
Chapter 5.1

References


