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Midgut carcinoids; surgical aspects, biogenic amines and vascular effects

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Future perspectives

Profiling the catecholamine production of a carcinoid tumor.

During surgery and on intensive care units, inotropic medication is routinely given in case of circulatory imbalance or failure. Inotropic medication may have adverse effects in case of a metastatic carcinoid patient, because it may further imbalance an otherwise already overbearing catecholamine system, resulting in a carcinoid crisis. Every carcinoid tumor may have a specific catecholamine profile that causes an imbalance or overshoot in circulating catecholamines. Especially patients with a history of a carcinoid crisis despite octreotide treatment will probably benefit from catecholamine profiling before surgery. Knowing the patients specific profile will enable tools for anesthesiology and intensive care medicine to choose the correct peri-operative inotropic medication for the carcinoid patient at risk of a life threatening (peri-operative) carcinoid crisis.

Understanding the cause of the carcinoid syndrome

During central vascular surgery facial flushes may occur after traction of the mesentery resembling carcinoid flushes in their distribution pattern. The mesenteric traction syndrome consists of hypotension, tachycardia and cutaneous hyperemia. The responsible factor in the mesenteric traction syndrome appeared to be Prostacyclin (PGI₂) as described by Gottlieb in 1988. These symptoms can be counter-measured by the cyclooxygenase inhibitor indomethacin. Our results with ex-vivo vascular ring perfusion, the use of indomethacin revealed marked differences in contraction by serotonin between carcinoid and control vascular rings (chapter 6b). Several studies report on elevated prostaglandins in carcinoid disease. It would therefore be interesting to investigate circulating PGI₂ and prostaglandins (metabolites) in vivo and vitro to clarify whether they are related to vascular imbalance, carcinoid syndrome or even a carcinoid crisis. Keeping in mind the mesenteric traction syndrome, it would also be interesting to investigate whether PGI₂ plays also a role in causing hot flushes.

Pre- and post-synaptic serotonin receptor (subtypes)

Although there is a considerable amount of data regarding the several subtypes of serotonin receptors distributed throughout the body, there is little knowledge about the receptor expression and the pre- and post-synaptic receptor activity in carcinoid patients. The persistent high levels

of circulating serotonin will probably downregulate receptors on several end organs. In the study with the ex-vivo vascular rings perfusion (chapter 6b) model, there appeared to be an alteration in the release of prostaglandins due to the loss of the pre-synaptic 5-HT_{3A} receptor function compared to control rings. In the control rings, contraction was partially mediated by prostaglandins. Indomethacin attenuated this response. Vascular imbalance (a prominent symptom of a carcinoid crisis) may be caused by loss of control by pre- and postsynaptic serotonin receptors as reflected in a disturbed baroreflex sensitivity. Further studies on pre- and postsynaptic configuration of serotonin receptors may be helpful in understanding the vasomotor imbalance in carcinoid patients.

Octreotide

To date we do not have a clear picture on the mechanisms involved in the peri-operative prophylactic effects of octreotide. In our study on peri-operative catecholamine production it became clear that octreotide did not prevent release of catecholamines. It was hypothesized that octreotide may exert its effect via stabilizing the end organ. As vascular imbalance is the major problem in a carcinoid crisis during surgery, it would be of interest to see if octreotide alters contractions in vascular ring perfusions as a first step in elucidating the pathways of octreotide prophylaxis.

Surgery in metastatic carcinoid

The last decades, especially since the advent of octreotide, surgery plays a more prominent role in the palliation of carcinoid disease. Most of the surgical interventions in the past were for small bowel obstruction. Nowadays the balance is gradually moving to cytoreductive procedures and more extensive mesenteric dissections to prevent bowel obstruction and/or vascular complications such as mesenteric vascular encasement. Less invasive techniques are gaining popularity. Radiofrequency ablation for liver metastases with or without laparoscopic support is a relatively new treatment modality. There are however no comparative data available on survival benefit. Tumor reductive surgery by means of a hemihepatectomie remains rare and the indications for an allogenic liver transplantation are still controversial, as the chances of cure by liver transplantation are still minimal. New palliative treatment modalities with more specific, targeted drugs resulting in a more chronic state may further improve the outcome of patients with metastatic carcinoid

disease. In this respect the results of phase II studies using bevacizumab, the VEGF-antibody and other anti-angiogenic compounds, are of interest. Hopefully these drugs can also induce responses that will make patients more amenable to surgical resection