Development of Addiction to Intranasal Fentanyl in a Cancer Patient

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Citation | Eid, M. (2018). Development of Addiction to Intranasal Fentanyl in a Cancer Patient. *Adiktologie*, 18(2), 129–131.

SUMMARY: The following case report describes the long-term comprehensive care of a patient with metastatic diffuse gastric cancer. In addition to chemotherapy, supportive care was especially important for the treatment of chronic abdominal pain, ileus, malnutrition, and iatrogen-induced addiction to intranasal opiates. The patient was in the parallel care of an oncologist and a nutritionist. Pain management was provided by the pain management centre and a psychiatrist. Because of the lack of information about opiate addiction in cancer patients, we had to cooperate very closely with specialists in pain management and addiction treatment. However, this intensive comprehensive care had only a partial effect. The daily dose of intranasal fentanyl in our patient was several times higher than the recommended maximum and relief from pain was only short and partial. This specific issue receives little attention in the literature. Nowadays, we have several new medication options and forms of application. Taking this into account, it will be very important to develop new recommendations for pain management in the near future.

Keywords | Palliative care – Gastric cancer – Intranasal opiates – Fentanyl – Iatrogen-induced addiction

Submitted | 8 March 2018 **Accepted |** 28 November 2018

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CASE REPORT

A 23-year-old patient was referred to our surgical outpatient clinic in November 2015 for unspecified abdominal pain, which she had experienced since January of that year. She had undergone a laparoscopic appendectomy, which revealed chronic appendicitis. Pancolonoscopy, with a suspected IBD finding, had also been performed because of the persisting problems. Subsequent GFS revealed stenosed pylorus and ulceration in the angulus. Endosonographic examination confirmed the infiltration of the gastric antrum and pylorus, the latter being impassable for the 12-mm instrument. Because of a suspected diffuse malignant infiltration, exploratory laparotomy including representative biopsy was performed in November 2015. Histology confirmed the diagnosis of diffuse gastric cancer with metastatic infiltration of mesentery and peritoneal carcinomatosis. Therefore, neither gastroenteroanastomosis nor jejunostomy was applied. No signs of an ileus condition were present at the time. It was decided that the patient would receive palliative chemotherapy administered by means of a central venous port. Nevertheless, severe ileus, associated with pyloric stenosis, developed during the postoperative period. This was eventually dealt with conservatively by using a drainage tube and total parenteral nutrition. To manage her abdominal pain, the patient was administered transdermal fentanyl in a basic dose of 12.5 ug with good effect. After her condition stabilised, the patient began to receive systemic chemotherapy mFOLFOX6. The patient tolerated the treatment very well. In addition, there was a partial response involving the restoration of the passage of the GIT. After the NG tube was removed, the patient could manage oral intake without major problems. In February 2016, the patient's condition worsened, this time with occasional vomiting. To manage breakthrough pain, 100ug intranasal fentanyl was administered in addition to the 25ug transdermal doses. As oral intake was impossible, total parenteral nutrition was resumed in the home-care setting. This procedure proved to be very effective; the patient showed very few symptoms within several days. Moreover, a restaging CT scan confirmed the stabilisation of the condition. The previous systemic treatment was therefore carried on, with even parenteral nutrition not being necessary. Around that time (April 2016) the excessive use of opiates, indicated especially by the more frequent application of intranasal fentanyl, was suspected for the first time. Taking this into account, it can hardly be ruled out that the previous symptoms were not due to opiate-induced paralytic ileus.

Another restaging CT performed in June 2016 confirmed the progression of the disease. The patient reported stronger abdominal pain and reduced oral intake because of the early sense of repletion and inappetence. The patient was referred to an outpatient nutrition centre for the resumption of parenteral nutrition to supplement oral intake. Pain was managed using a 10/5mg oxycodone/naloxone combination administered every 12 hours and sublingual 133ug fentanyl, when necessary to alleviate breakthrough pain, with butylscopolamine tablets taken every eight hours. Transdermal opiate patches were not indicated because of the previous passage complications. We wanted to avoid the intranasal route of administration given the suspicion of abuse. In view of the progression of the underlying disease and PS1, on 21 June 2016 the patient commenced a second-line palliative therapy involving a combination of paclitaxel and ramucirumab.

The patient tolerated the second-line treatment well. However, since August 2016 her consumption of opiates had grown. The patient refused the sublingual form of fentanyl because of its insufficient effect, despite the increase in patch doses. Although recommended to do so, she did not use the oxycodone/naloxone tablet combination on a regular basis and wanted to return to intranasal fentanyl because of the rapid onset of its effect and its very good toleration. Moreover, the patient experienced intermittent episodes of reduced oral intake, nausea, and vomiting, during which she depended on total parenteral nutrition provided in the home care setting. On other days, she managed to consume supplementary sip feeds and minced food in addition to PN. At that time her pain management was changed to the application of 25ug transdermal opiate (fentanyl) patches, and, respecting the patient's preferences, we proceeded to use 100ug intranasal fentanyl spray to treat breakthrough pain. However, this led to the development of the excessive use of the intranasal opiate, with the patient, despite repeated advice and an increase in the transdermal opiate dose to 50ug, applying the spray 20 times per day (one shot each time), and the dosage tended to grow. By the end of 2016 she was consuming two vials of 200ug fentanyl (40 doses) per day. She had been shortening the intervals between applications because of very frequent stabbing pain (VAS 7-10/10), which reached its greatest intensity during the night and met the definition of breakthrough pain. 20/10mg oxycodone/naloxone tablets taken every 12 hours were included in the medication again, with the dosage being increased to 40/20 mg 1-0-1 to 1-0-2 because of persisting abdominal pain. We also tried buccal fentanyl tablets, again only temporarily, but with no major effect on the patient. Despite the risk of ileus, as it was not possible to reduce the dosage, we gradually increased the dose of transdermal fentanyl to 150ug in order to reduce the number of intranasal applications. Even with the transdermal dose being heightened, no deterioration of passage problems was observed. Nevertheless, the patient still suffered from severe pain, largely localised in the epigastric and right iliac fossa areas. With her consent, the patient was referred to the inpatient psychiatric ward, where efforts were made to adjust the medication using anxiolytics and antidepressants with the purpose of limiting the application of intranasal fentanyl. The effect was short-term only; for two weeks the patient was back to 40 doses of 200ug fentanyl, i.e. one vial per day.

In February 2017 the patient underwent another restaging CT scan, which showed a stabilisation of the disease. She continued to receive the systemic paclitaxel-plus-ramucirumab-based treatment, managed to take in orally only a very small amount of mixed food, and was provided with nutrition mainly parenterally using Smofkabiven bags (1800 ml daily). Vomiting was intermittent. The patient re-

peatedly rejected the drainage tube. Paracentesis was performed repeatedly on an outpatient basis to remove refractory ascites. A combination of 150ug transdermal fentanyl, 40/20 mg oxycodone/naloxone 1-0-2 to 2-0-2, and 200ug intranasal fentanyl in a massive quantity of 80-100 doses per day provided the patient with at least satisfactory palliative treatment for her extensive malignant disease. Additionally, a central venous access made it possible to apply 5ml metamizole infusions in the home setting once to twice daily, as needed.

In early April 2017 the patient was admitted to the inpatient oncology ward after her clinical condition worsened dramatically. Three days later, 16 months after being diagnosed with metastatic gastric cancer, the patient died.

DISCUSSION

Out of the medication used to manage breakthrough pain, intranasal fentanyl was found to show the best outcomes as regards the speed of its onset, the duration of its effect, and the profile of its adverse effects, such as hallucinations, nausea, and confusion (Zeppetella, 2014). However, iatrogen-induced addiction and tolerance to such high doses have not been dealt with in the literature, as the development of addiction was not the issue of primary interest among patients with anticipated short-term survival. Given the increasing use of intranasal opiates, nevertheless, the above case report may not represent an isolated episode. It suggests that these aspects should be taken into consideration when choosing therapies to manage breakthrough pain.

CONCLUSION

Finding an effective pain management regimen and iatrogen-induced addiction to intranasal fentanyl were the major complications in the treatment of this young patient. Despite maximum effort, in this particular case it was not possible to switch the patient to transdermal opiate medication in order to at least reduce the consumption of intranasal fentanyl. A combination of transdermal and intranasal fentanyl, oxycodone/naloxone tablets, intravenous metamizole, and anxiolytics and antidepressants provided at least some pain management and an improvement in the patient's quality of life, although the cost of such treatment is exorbitant. Bearing in mind the poor prognosis and expected survival, the patient's comfort and quality of life should, however, be the central consideration. Supportive treatment management was greatly facilitated by the outpatient nutrition centre, which, among other assistance, assured regular prescriptions of home parenteral nutrition. This was administered in cooperation with a home care service.

Authors' contribution: M. E.: Case report. D. B.: Discussion and Conclusion. S. D. : Consultation of a psychiatrist.

Conflict of interest: None.

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