

# The Combination of Pain and Aggression - Two Impressive and Representative Case Reports

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## Abstract

**Background:** It is widely accepted that manifestations of pain cannot be detached from the case history, accompanying diseases, and the individual medication profile. An indirect association between pain and aggression (due to psychosis) as a cause of administration of neuroleptics has not been described yet.

**Aim & method:** Here we report the connection between treatment of pain and additional medication with a neuroleptic for patients with manifest aggression and psychotic background in two impressive cases.

## Course & outcome:

**Case 1:** A 57-year-old male patient underwent surgery for an esophageal carcinoma. Since the second postoperative day, the patient had been given long acting morphine orally. After several days, the patient became verbally aggressive. As he was suffering from a depression, he was administered higher doses of neuroleptics. As a consequence, his pain and aggression were reduced significantly and permanently.

**Case 2:** A 24-year-old male patient was surgically treated for colon carcinoma. He complained about abdominal pain. Under long acting tilidine 50mg, pain increased. Increasing dosage had no effect. However, intensity of pain (NRS 10) could only be reduced to NRS 2 by piritramide (7.5mg). Despite of the lack of psychotic disorders in the past the patient became verbally aggressive. Presuming a reactive psychosis, an administered neuroleptic reduced pain and aggression effectively and permanently.

**Conclusion:** If administration of painkillers does not lead to an adequate reduction of pain in the patient, and if an accompanying psychosis is present or suspected, this can manifest as aggression, an additional administration of neuroleptics needs to be considered.

Received date: February 03, 2016

Accepted date: February 26, 2016

Published date: February 27, 2016

**Citation:** Brinkers, M., et al The Combination of Pain and Aggression - Two Impressive and Representative Case Reports. (2016) J Anesth Surg 3(1): 102- 105

DOI: 10.15436/2377-1364.16.032

**Keywords:** Cancer; Pain Therapy; Psychosis; Aggression; Interdisciplinary approach.



## Introduction

A direct connection between pain and aggression due to psychosis as a cause to prescribe neuroleptics has not been described until now. It is usually assumed that aggression arises from the untreated pain. For that reason, pain is always treated with analgesics<sup>[1]</sup>. However, aggression with increased depressive affliction is also possible in patients without neoplasms<sup>[2]</sup>.

The concomitant medication with highly potent neuroleptic agents has been previously described but typically when aggression arises in the context of dementia<sup>[3]</sup>, intellectual disability<sup>[4]</sup> or schizophrenia<sup>[5]</sup>. Moreover, it is necessary to differentiate be-



tween cause and manifestation of aggression. Verbal aggression as a result of insufficient treatment with analgesics in the context of the algogenic psychic syndrome can be treated adequately with painkillers. Aggression on the basis of psychosis is practically untreatable with analgesics and requires the administration of neuroleptics<sup>[4]</sup>.

If the reduction of pain is slow or has no lasting effects and accusations from the patient itself or relatives arise, this may lead to dimensions in which a trusting collaboration is disturbed. In extreme cases, that can result in aggressive behavior of the involved parties. This situation can be triggered by an information deficit along the lines of “what is the further plan for pain therapy”. We present two cases in which alternating the medication of the patient reduced the pain trigger, the aggressiveness and thereby deescalating the situation (Table 1).

<b>Case 1:</b> Born 1957, July Caucasian male, married, retired	<b>Case 2:</b> Born 1990, April Caucasian male, single
<b>Primary Diagnosis:</b> Esophageal cancer (cT3cN1cMxG2), neo-adjuvant radio-chemotherapy	<b>Primary Diagnosis:</b> carcinoma left hemicolon; 3 surgical interventions so far; last end 2014: multi-visceral resection; currently suspected multiple lymphogenic metastases
<b>Secondary Diagnoses:</b> Achalasia, biliary pancreatitis, cholecystectomy 2014, Juli; myasthenia gravis, thymectomy 1987, depression	<b>Secondary Diagnoses:</b> Pneumonia in both lower lobes; previous one-sided nephrectomy
<b>Current medication:</b> Duloxetine 60, 1x1 Fluoxetine 20, 2x1 Melperone 25mg, at night Pyridostigmine 3x120mg Quetiapine prolong 150 at night (not noted during primary consultation) Pantoprazole 40, 1x1	<b>Current medication:</b> Ampicillin/Sulbactam 375mg, 2x2 Clarithromycin 500mg, 2x1 Iron Supplement Pantoprazole 40, 1x1 N-acetylcysteine 600mg, 1x1 Amphotericin B Suspension, 3x/d Analgesics when required

### Case Reports:

(I) A male patient, born 1957, with esophageal cancer was presented after neo-adjuvant radio-chemotherapy and achalasia, and with a history of myasthenia gravis. After esophageal resection, he was treated with ropivacaine 0,375%, 8ml/h via an epidural catheter for a total of five days. On the first post-operative day he was satisfied with this treatment.

On post-operative day two, an additional infusion with i.v. morphine (20mg/24h) was added, reducing the pain level to numerical rating scale (NRS) 1.

On the fourth post-operative day, the continuous morphine infusion was stopped and changed to subcutaneous morphine. The epidural was discontinued on day six and the patient received morphine 60mg every 8h (the cumulative daily dose of the infusion plus 80mg/d morphine, which the patient had already received prior to surgery), with the possibility of claiming

10mg morphine up to ten times daily. However, this regimen resulted in steadily increasing levels of pain, and the ward staff became anxious. The epidural therapy was therefore restarted with ropivacaine 0.2%, 8ml/h. From noon onwards, the ward staff contacted the pain consultant every 15 minutes, as no sufficient pain reduction was observed.

A senior anesthesia attending examined the patient and administered a cumulative dose of 30mg morphine intravenously, which resulted in sufficient pain control. However, pain reduction lasted only until next morning. Therefore, a specialized pain therapist visited the patient, after discussing the case with a psychiatrist in the pain clinic.

The patient history and psychiatric evaluation revealed no thought disorder or disarray in perception or concentration. Yet the patient was angry, irritable and verbally aggressive concerning the unsuccessful pain therapy. The tumor surgery in combination with pain acted as an amplifier to the delusional certainty of “pain as punishment” for past misconduct. Yet the patient could follow questioning and understood the suggestions of the pain therapist.

The patient’s history also revealed that he did not only use long-acting morphine prior to surgery but also that he was in psychiatric care for psychotic conditions. According to the patient, he was treated for delusional depression and had taken a strong neuroleptic prior to hospital admission (quetiapine 50 - 0 - 150 mg). This medication was now augmented with a higher dose of quetiapine (50 - 0 - 250 mg). In addition, lorazepam (3 x 1 mg) was prescribed.

The patient was informed about the change of the therapeutic regimen, and the relation to his unsatisfactory pain management was discussed. Under the new medication, no exacerbations of pain occurred.

(II) A male patient, born 1990, with lymphatic metastases of a hereditary colon carcinoma, was presented to the pain consultant by the surgical team after right-sided hemicolectomy and splenectomy, currently under chemotherapy.

A few days prior, the patient was treated in the pain department by request from the surgical team. At this first contact, the up until then opioid-naïve patient received tilidine, 3 x 50mg/d. This regimen had to be augmented to 3 x 100mg/d, for the reason of increasing pain within the next few days. Later the patient was emergently admitted to the hospital with massive pain (NRS = 10). Piritramide, 7.5mg (a synthetic opioid of 0.66 morphine equivalent = 5mg morphine), administered subcutaneously was sufficient to reduce pain to NRS 2.

When the patient was presented as an inpatient to the pain consultant, the tilidine dose was increased to 3 x 150 mg per day and, additionally, lorazepam 3 x 0.5 mg/d was prescribed.

During the following night the pain increased again. The patient’s relatives voiced accusations against the resident physician because of this. The case was conveyed to the pain service. The repeated, now stat pain consult, looked at possibilities of an efficient and effective, meaning continuing, pain reduction and discussed the possible background relating to the pain: The patient is a single child; the parents have feelings of guilt arising from the hereditary nature of the tumor; extensive fears because the patient may die at young age before the parents. The patient prior to admission voiced these fears but they increased parallel to the pain during the hospital stay.

During the following night, pain increased again, which

led to a further application of 7.5mg piritramide subcutaneously. Only the additional prescription of the neuroleptic risperidone (2x0.5mg/d) in addition to 3x0.5mg of lorazepam resulted in a substantial pain reduction. Since then the patient complained of no pain.

## Discussion

Especially from a surgical point of view, the interdisciplinary approach is frequently emphasized<sup>[6]</sup>. One can often find this philosophy lived on a daily basis, as particularly surgical colleagues often adhere to interdisciplinary consensus and actively implement decisions.

This can be demonstrated not least in a consultant service, for example at the University Hospital Magdeburg, where pain clinic has elementary traits of a liaison service, as physicians and nursing staff of the respective ward are included by the consultant in finding therapy options and in finding final decisions. This is aided by the, often repeated, presence of the pain consultant until the patient is satisfied with pain management. The surgeons allow the consultant liberty to treat these specific patients. This proven collaboration has an interdisciplinary goal of rapidly and efficiently setting pain medication in the perioperative and interventional course of every single patient, latest up until the day of discharge.

It is widely accepted that pain manifestations cannot be regarded outside of the patient history including current comorbidities, current phase of treatment (for example perioperative/-interventional), or the individual medication profile. In both presented cases aggressive behavior occurred due to dissatisfaction regarding attained therapy (concerning pain reduction). In review, the reason for the aggressive behavior was found in psychiatric comorbidities. However, there is only one newer study regarding aggression, mental pain, communication and suicidal tendency; but this addresses self-aggression in psychiatric patients and not hostility in surgical patients<sup>[7]</sup>.

In the first case the patient's psychoses was already established and exacerbated because of growing pain. An increase in dosing of the neuroleptic and additional prescription of lorazepam relieved the situation for the patient within a day.

For this reason, the relationship towards the different parties (nurses, surgical team, and anesthesia team) also improved. The experience, that an exacerbated psychosis can increase pain to the level where opioids in excess of 500mg morphine are insufficient, is one we have met previously<sup>[1]</sup>. The bottom line is that an increased dose of the neuroleptic plus additional benzodiazepine exerts a better effect on treating the pain than increasing the opioids alone. The reason can be found in treating the psychosis and with that the fears of the patient.

In the second case, an excessive history and psychiatric exploration was done in the pain clinic prior to the patient's admittance. A pre-existing psychosis was not found. Despite this, the patient was also treated with a highly potent neuroleptic and a benzodiazepine. Likewise, this resulted not only in a reduced level of pain for the patient but also deescalated the tense situation on the ward within some hours.

There are limitations in efficacy of pain therapy, such as insufficient dosage, preexisting opioid abuse, noncompliance, and severe somatic disorders. However, sufficient administration of morphine in case 1 and of tilidine/piritramide in case 2

did not result in an adequate reduction of pain in both patients. The fact that under  $3 \times 150$  mg tilidine the pain level reached NRS 10, but 7.5mg of subcutaneous piritramide, the equivalent of 5mg of morphine = 50 mg tilidine, reduced the pain level to NRS 2, points to a significant psychiatric component. Of great interest was the observation that a 30-minute conversation with the patient had the same effect on pain reduction.

During the first outpatient contact the suspicion arose that the parents of the patient had strong feelings of guilt due to the hereditary tumor, and that they did not know how to deal with the imminent death of their son. This situation made them prone for quick assignments of guilt against third parties. One can contemplate that what was seen here is what the Scandinavian literature calls a "Reactive Psychosis"<sup>[8]</sup>. It follows the assumption that an incident (tumor *plus* pain) only has to build up enough psychotic pressure, resulting in psychosis-like symptoms in a patient. That this happened with the patient cannot be surely proven but can be assumed due to the positive reaction to the highly potent neuroleptic agent.

Both cases presented here are of patients with a tumor, which we don't see as a coincidence. It can be assumed that the neoplasms act as an amplifier for pain and exacerbation of psychosis<sup>[1]</sup>. Through their tendency for deterioration, they pose a very specific and therapeutically exploitable trigger of aggression.

Interestingly, the cause of aggression was also different in both cases. In the first, the aggression arose on basis of a delusional depression and the certainty that the current tumor is a punishment for past misconduct. In the second case, aggression occurred out of overpowering despair and the fear of imminent death. This spectrum of reasons for aggression poses a connection between the psychopathologic disease pole and the biological therapy pole.

It can be assumed that aggression is a reactive behavior towards fury and despair<sup>[9]</sup>, and despair can be alleviated or augmented through support given or denied by the family or the ward staff and therefore poses an important factor in the reduction of aggression<sup>[2]</sup>.

In addition, a dysfunction of the endogenous opioid system is hypothesized as a mechanism of aggression<sup>[10]</sup>. The chemical relationship between neuroleptics and opioids is well established, and is the reason that both of them can influence pain as well as fear and fury<sup>[11]</sup>.

## Summary

To our knowledge, there are no reports of patients suffering from pain, depression and exhibiting a high level of verbal aggression. This combination requires a team of anesthesiologists specialized in pain therapy as well as psychiatry expertise. So from our point of view and drawing from past experience with manifest aggression in pain patients like those in the presented cases, the following algorithm can be proposed as a basis for future effective patient management and efficient communication between interdisciplinary teams [i.e. surgery and pain therapy/anesthesiology] as well as patients and relatives.

If a patient suffers from severe pain, which is unsusceptible to increased oral opioid dosing, at first an i.v. titration with an opioid should be attempted. Psychotropic drugs should be considered in the special case of psychosis with severe hostility. However, a missing response to painkillers often leads to

aggressive behavior. Aside from the prescription of lorazepam, the prescription of a highly potent neuroleptic [i.e. 2×0.5mg risperidone] is always indicated.

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