Scandinavian Journal of Pain 17 (2017) 189–190

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

A case-history illustrates importance of knowledge of drug-interactions when pain-patients are prescribed non-pain drugs for co-morbidities

Harald Breivik[a,b,c,*]

[a] University of Oslo, Faculty of Medicine, Oslo, Norway
[b] Oslo University Hospital, Department of Pain Management and Research, Oslo, Norway
[c] Oslo University Hospital, Department of Anaesthesiology, Oslo, Norway

In this issue of the *Scandinavian Journal of Pain* Vigdis Solhaug and Espen Molden publish an interesting and important review of negative interactions between drugs we prescribe for patients suffering from chronic pain and other, non-pain drugs that patients take for other health problems [1]. They also describe how our genes can cause major differences in how individual patients react differently to analgesic drugs [1]. After one of Professor Espen Molden's informative lectures on these topics, we discussed how we can understand the following conundrum in this chronic pain patient's history:

1. An educational patient history

This 72 year old lady had multiple painful degenerative changes in her back, also a narrow spinal nerve canal at L2, causing radiating pain to her left hip and thigh region, our experienced neurosurgeon considered that her degenerated osteoporotic back skeleton would make it too risky to try to operate, even with micro-surgical technique. She also has a constantly painful left knee and leg after failed surgery for a fractured tibia; she developed a compartment syndrome, but this was not diagnosed until several extremely painful days later, and too late to save leg muscles. She has been wheel-chair bound for more than 15 years. However, at home she was actively moving around with two crutches.

When she was referred to the Department of Pain Management and Research at Oslo University Hospital, her three main problems were (1) "nodding", she fell asleep after a few minutes conversations with friends and relatives, being extremely sleepy all day so that social activities were almost impossible. (2) Extreme constipation almost unresponsive to large doses of various laxatives. (3) Hyperhidrosis, causing her bed to be wet in the morning and necessitating change of wet garments during the day.

From her general physician (GP) and from consultations with various specialists she was prescribed and used the following drugs:

Fentanyl patch 100 μg/h gave her reasonable pain relief when in her wheel-chair, but any activity outside the wheel-chair would precipitate severe pain attacks in her back, hip and knee, all on her left side.
Pregabalin 450 mg daily for her back and knee pain
Diclofenac 50 mg × 3 daily for pain
Lanzoprazol 30 mg × 2 (sic) daily was effective in keeping her acid-dyspepsia under control
Atorvastatin 40 mg daily for reducing cholesterol
Acetylsalicylic acid 75 mg daily after a carotid artery stenosis-plaque-operation for transient ischaemic attacks (TIA) about 5 years ago.

We diagnosed several complications of her analgesic drugs:

(1) The extreme sleepiness and "nodding" caused by fentanyl and probably made worse by her high dose pregabalin (measured in the "toxic" plasma-concentration range)
(2) She clearly had a severe opioid-induced constipation (OIC), probably also opioid delayed gastric emptying of acid stomach content (from diclofenac, acetylsalicylic acid) so that she had to take the proton-pump-inhibitor (PPI) lanzoprazol.
(3) She had sever hyperhidrosis induced by the fentanyl.
(4) Cystatin C-based estimate of her kidney-function (GFR) documented that she has a significant kidney problem with eGFR only 33 ml/min, probably caused, or aggravated, by several years of high dose diclofenac.

2. Treatment

The easiest complication to "fix", we reckoned, was her OIC because we now had available the PAMORA (peripherally acting

DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2017.09.009.
* Corresponding author at: Oslo University Hospital, Department of Pain Management and Research, Pbox 4956 Nydalen, 0424 Oslo, Norway. Tel.: +47 23073691; fax: +47 23073690.
E-mail address: harald.breivik@medisin.uio.no

https://doi.org/10.1016/j.sjpain.2017.09.023

my-opioid receptor antagonist) naloxegol. We prescribed naloxegol tablets 25 mg to be taken in the morning. We warned her that she should be close to the toilet. Naloxegol promptly caused a forceful bowel movement, and in spite of our warning, her wheelchair-problem made it too difficult for her to get to the toilet in time!

She continued taking naloxegol tablets every second day, taking the 25 mg tablet when she was already sitting safely on the toilet chair. This continued to help her empty her bowels well.

However, she complained that she felt "terrible", her pain increased in intensity and also the attacks of radiating pain from her L2-root came more often. This did not make sense as she had continued with the transdermal fentanyl 100 μg/h administrations. She continued to feel "lousy" and therefore she stopped using the naloxegol tablets. After a few days without this peripherally acting my-opioid-antagonist, pain relief improved and her constipation worsened.

3. For some reason her naloxegol penetrated her blood–brain–barrier (BBB) and caused opioid withdrawal

After consulting Professor Molden, we had the following likely explanation to this conundrum: Naloxegol is a large molecule that should not easily penetrate to the inside of the BBB. More important was probably that naloxegol is kept outside the BBB mostly by the Permeability-glycoprotein-transporter (Pgp) located in the endothelial cells of capillaries at the outside of the BBB. The activity of the Pgp is inhibited by several other drugs (see Table 1 in the Solhaug and Molden paper in this issue [1]), and in her case the lanzoprazol (a PPI) as well as the statin atorvastatin, both are Pgp-inhibitors. These two inhibitors of the Pgp made it possible for naloxegol to penetrate the BBB, enough to cause clear clinical withdrawal symptoms for this patient. Renal impairment is another factor that can reduce the efficacy of the Pgp at the BBB [1].

We discontinued her diclofenac which is a likely cause of her renal impairment and also contributed to her very acid gastric content. We discontinued her statin, which contributed to her generalized muscle pain, and her lipid profile kept normal without this potent drug.

And we reduced the dose of pregabalin to 75 mg × 2 daily. Pregabalin is mostly excreted by the kidneys, explaining her toxic plasma-concentrations, and with this much reduced dose her plasma-concentration was normalized. This clearly contributed to her "awakening".

We converted her high dose of fentanyl patch to sublingual buprenorphine, 1 mg Temgesic resoriblets daily. Buprenorphine is NOT excreted by the kidneys and is therefore an ideal opioid analgesic for patients with renal impairment. Buprenorphine has less sedative effects, less respiratory depressive effect. Buprenorphine also has less negative effects on endocrine organs than most other my-opioid-receptor agonists, less negative effect on androgen hormones, especially testosterone. Testosterone is well documented to decrease pain sensitivity and increase pain-tolerance. Buprenorphine is the ideal opioid for this patient [2,3]. For this patient buprenorphine 1 mg/24h had superior pain relief with less side-effects than fentanyl 2.4 mg/24 h plus diclofenac 150 mg/24 h (!).

This agrees well with her continued satisfaction with her pain-relief. She sleeps better at night, with less opioid aggravated obstructive sleep apnoea. Her cognitive functions are back to her normal. She has almost normal bowel movements and need laxatives only occasionally. She is more than satisfied with pain management at the Department of Pain Management and Research at Oslo University Hospital, also because we were able to understand her complex pharmacological drug interactions better, thanks to help from Professor Espen Molden [1]

Ethical issues

The patient agreed to the publication of her pain history and pain management.

Conflict of interest

None declared.

References

[1] Solhaug V, Molden E. Individual variability in clinical effect and tolerability of opioid analgesics – importance of drug interactions and pharmacogenetics. Scand J Pain 2017;17:193–200.
[2] Butler S. Buprenorphine – clinically useful but often misunderstood. Scand J Pain 2013;4:148–52.
[3] Breivik H. Buprenorphine – the ideal drug for most clinical indications for an opioid? Scand J Pain 2013;4:146–7.