



Editorial comment

The burden of central anticholinergic drugs increases pain and cognitive dysfunction. More knowledge about drug-interactions needed

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In this issue of the *Scandinavian Journal of Pain*, Flavia Karine Rigo and co-workers in Brazil report on their studies that revealed a cholinergic mechanism of the antinociceptive action of a peptide from a spider-toxin [1]. Their study is well done and well reported, following the ARRIVE-recommendations for doing and reporting animal research [2]. They found that in a chronic nerve/nerve-root constriction model (model of neuropathic pain) this peptide causes a robust reduction in mechanical withdrawal (~reduction of neuropathic pain), and in pain caused by paw-injection of capsaicin [1]. The mechanism of this effect was clearly demonstrated to be via inhibiting acetylcholine-esterase (AChE) in the CNS (spinal cord). Being a peptide, they had to inject this peptide intrathecally (IT), directly in to the cerebrospinal fluid (CSF).

1. More attention needed on benefits of cholinergic drugs and on the negative effects on cognitive functions and pain from anticholinergic drugs

We publish their study-report [1] also because clinicians need more knowledge and attention to the *beneficial effects on cognitive functions and pain by cholinergic drugs*, but even more so we need more knowledge about the *burden of the multitude of anticholinergic drugs*. Patients suffering from pain, especially our elderly patients, are often exposed to anticholinergic drugs [3]. Anticholinergic drugs may have direct, or indirect, blocking effects on acetylcholine receptors in the CNS and on the autonomic nervous system. Atropine and scopolamine are the classic, anti-acetylcholine drugs that most clinicians can relate to, causing dry mouth and rapid heart rate. In larger doses of atropine than the 0.5–1 mg used before and during general anaesthesia, will make the patient drowsy, but even larger doses as used in psychiatry for “atropine-shock”

treatment (not used any more) caused a rapid onset, deep central anticholinergic syndrome with rapidly decreasing conscience, myoclonic tremor and twitching due to peripheral neuro-muscular effects, large pupil size (the “bella donna” pupil), after some time the patient was in deep coma. When the temperature increased, the patient could develop severe “malignant” hyperthermia, and the patients were rapidly awakened by physostigmine given intravenously [4].

2. Cholinergic drugs

Physostigmine, like neostigmine, is a potent acetylcholinesterase inhibitor, increasing the amount of acetylcholine at the cholinergic receptors. Neostigmine does not cross the blood-brain-barrier (BBB), partly because it is a quaternary amide, partly because the *Permeability-glycoprotein (Pgp)* on the capillary side of the BBB keeps neostigmine outside the BBB.

There has been impressive research-efforts by James Eisenach and his co-workers on neostigmine administered IT or epidurally in patients having spinal or epidural analgesia, and there is no doubt that neostigmine by inhibiting AChE in the spinal cord and other parts of the CNS has analgesic effects on acute post-operative nociceptive pain and obstetric pain, but also on more chronic neuropathic pain [5,6]. Neostigmine has an additive, possibly even supra-additive (synergistic) effect on pain-relief when co-administered with an opioid analgesic or with an α_2 -agonist such as clonidine [5]. Unfortunately, neostigmine causes nausea often enough to discourage its routine use. However, these many studies on neostigmine has documented beyond any doubt that AChE inhibitors that can cross the BBB will enhance pain-relieving mechanisms in the human central nervous system [5,6]. This is even more important now that opioid analgesics, after a period with uncritical marketing and prescribing opioids for chronic pain *without appropriate monitoring*, opioid-prescription now are subject to increasing restrictions from health authorities. This development makes it necessary for all of us to look for other effective and less risky alternatives to opioid analgesics.

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3. Anticholinergic drugs: cognitive dysfunction, pain, risk for falls, and increased mortality

Many of the drugs commonly prescribed to elderly, co-morbid patients, have direct or indirect anticholinergic effects [7]. When two or more drugs with anticholinergic effects are co-administered, the patients develop somatic dysfunctions, cognitive impairment, and behavioural disturbances [8]. One not uncommon result is that an early, minor cognitive decline, hardly noticeable by relatives, will accelerate. The diagnosis of dementia is erroneously made, and treatment adjusted accordingly. No doubt this is a major and unnecessary burden to our elderly persons. The complex symptoms and signs of an ongoing anticholinergic burden from multiple drugs unfortunately can end in falls, and all-cause mortality increases [9]. An additional problem for these patients is their inability to communicate their pain and discomfort to those caring for them [10].

The early antidepressive drugs, the tricyclic (TCA), especially amitriptyline, have potent anticholinergic effects [11]. At the times when we saw TCA-intoxication from suicide attempts, the patients had very typical central anticholinergic symptoms; Drowsy, sleepy, in and out of unconsciousness, irregular tachycardia and other heart arrhythmias, often pronounced myoclonic contractions (mistakenly diagnosed as epileptic seizures and treated with benzodiazepines, making the patients more deeply unconscious). When we had a chance to give physostigmine 1–2 mg IV, the tremor and myoclonic twitching disappeared and the patients woke up, but fell into coma again after 0.5–1 hour. This demonstrated very clearly that the patient had a central anticholinergic syndrome [4].

4. Amitriptyline for chronic pain

The most authoritative guidelines for pharmacological treatment of neuropathic pain list amitriptyline as a first line drug [12]. The daily doses studied were 75 mg, 100 mg, or 150 mg.

Although the analgesic effect of amitriptyline comes sooner and at lower doses than what are needed for antidepressive effect, doses of amitriptyline up to 150 mg are high enough to cause significant anticholinergic effects, with drowsiness and clearly hypnotic, sedative effect. It is this anticholinergic sedative effect that makes chronic pain patients take their amitriptyline at night. Most patients still feel drowsy and sleepy next morning, often until lunchtime.

If the patient is prescribed another drug with anticholinergic effects, such as alimemazine (Vallergran®) for sleep, the negative central anticholinergic effects can cause severe cognitive dysfunction, memory-loss, and any analgesic effect of the TCA will be neutralized or antagonized.

5. Drugs with anticholinergic effects [3] should be avoided in patients on amitriptyline [3]

High anticholinergic activities: Alimemazine, clozapine, dicyclomine, doxepin, L-hyoscyamine, thioridazine, and tolterodine

Moderately high anticholinergic activities: Chlorpromazine, diphenhydramine, nortriptyline, olanzapine, oxybutynin, and paroxetine.

Some anticholinergic activities: Citalopram, escitalopram, fluoxetine, lithium, mirtazapine, quetiapine, ranitidine, and temazepam.

Anticholinergic activities only at higher doses: Amoxicillin, celecoxib, cephalexin, diazepam, digoxin, diphenoxylate, duloxetine, fentanyl, furosemide, hydrocodone, lansoprazole, levofloxacin, metformin, phenytoin, propoxyphene, and topiramate

6. Management of chronic pain with cholinergic drugs: Any of the inhibitors of acetylcholine-esterase (AChE) that can penetrate the blood-brain-barrier (BBB)?

Physostigmine is an inhibitor of AChE and can easily cross the BBB. For anaesthesiologists and nurse anaesthetists able to use physostigmine during the wake-up period of general anaesthesia can observe how the patients wake up, rapidly and completely and generally feel little or no pain. This effect has been demonstrated in randomized, double blinded, placebo-controlled studies, e.g. in Uppsala in Lars Wiklund's and Torsten Gordh's research groups [13]. Physostigmine has a short duration of effect. It may be necessary to administer physostigmine by continuous IV infusion.

Physostigmine is mostly used by the anaesthesia team and in some places by nurses in the Post-Anaesthesia-Care-Unit (PACU). It deserves more attention by GPs and gerontologists.

Donepezil (Aricept®) is an inhibitor of AChE in the CNS, causes some improvement in cognitive functions and donepezil is indicated for patients with early dementia, delaying the progress of this unfortunate disease.

Donepezil was documented to improve relief of chronic neuropathic pain when co-administered with gabapentin in an explanatory, pilot-type study in Uppsala [14]. Two more publications support this additive effect of donepezil for chronic pain [15,16]. They observed only few and moderately intense adverse effects, mostly from the gastrointestinal system (nausea, diarrhoea).

Neostigmine does not penetrate the BBB and has to be administered intrathecally (or epidurally from where it diffuses through the dura and arachnoidea). Unfortunately there is a risk of nausea and even vomiting. Therefore neostigmine appears not to be a good drug for creating antinociceptive cholinergic effects.

The **peptide** isolated from spider-toxin has not been studied in humans, and has the same disadvantage as neostigmine: It must be administered intrathecally [1].

7. Conclusion

Drugs with ANTicholinergic effects should be avoided as much as possible in patients suffering from chronic pain. Strengthening CHOLINERGIC mechanisms in our central nervous system is a documented mechanism for relieving pain, but we have few drugs of this class available for treating pain [1,5,15,16]. The ongoing opioid crisis in the USA has the important effect that there are renewed and strengthened efforts to find non-opioid analgesic drugs. This should strengthen James Eisenach's hope from almost 10 years ago [5]: "Thus, muscarinic cholinergic agonists and cholinesterase inhibitors hold promise as non-opioid agents for the treatment of moderate to severe acute and chronic pain"

Conflict of interest

None declared.

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