Long-acting injectable olanzapine can give rise to a condition consistent with central anticholinergic syndrome

Central anticholinergic syndrome can be life-threatening. The condition can occur as a result of unintended strong anticholinergic actions of a range of drugs. In rare cases, injection of olanzapine pamoate can give rise to a condition marked by delirium and sedation that is consistent with this syndrome. In cases of central anticholinergic syndrome, physostigmine is an effective antidote. Physostigmine is reported to give a good response in cases of oral overdose of olanzapine. Treatment with physostigmine should be considered if delirium and sedation occur following injection of olanzapine.

Acetylcholine and its receptors are abundant in the central nervous system. Acetylcholine activates two distinct types of cholinergic receptors: muscarine-sensitive (muscarinic) and nicotine-sensitive (nicotinic). Central anticholinergic syndrome occurs as a result of blockade of muscarinic acetylcholine receptors in the central nervous system. The symptomatology is complex and the condition can easily be overlooked, especially postoperatively. The diagnosis is based on clinical signs and symptoms, exclusion of other conditions, and the alleviation of symptoms by the use of physostigmine (1, 2). The syndrome was more common when scopolamine and atropine were used as premedication before general anaesthesia. Previously, the condition has been called «postoperative delirium», «atropine poisoning» and «anticholinergic syndrome» (2). Central anticholinergic syndrome is described in the psychiatric, accident and emergency, and anaesthesiology literature. But, as mentioned, it is a condition that is easy to overlook, and it has therefore also been called «the forgotten diagnosis» (2).

Effects of physostigmine

Physostigmine inhibits the breakdown of acetylcholine, thereby increasing the level of acetylcholine at cholinergic synapses. The drug crosses the blood-brain-barrier and quickly produces central effects. It will therefore reverse both central and peripheral effects of atropine, scopolamine and many other drugs with anticholinergic properties (3). Increasing doses of physostigmine can give rise to markedly increased salivation, bradycardia, seizures, and loss of control of bladder and bowel, as well as of the respiratory muscles leading to death by suffocation (2). As a rule, atropine will successfully reverse the poisoning, but other measures that stimulate the circulation and respiration may be required (2).

Physostigmine as an antidote

The effect of physostigmine with regards to atropine poisoning has been known for about 150 years (1, 4). In 1976, Rupreht & Dworacek presented a detailed review of the treatment of more than 200 cases of central anticholinergic syndrome in which physostigmine was used (5). Despite this, knowledge of physostigmine as an antidote to central cholinergic syndrome is remarkably limited (1, 4). Even the most recent editions of major pharmacology textbooks include only a very brief discussion of it (3). In an investigation into antidote preparedness of hospitals in Norway, Solheim and colleagues found that only around 80 % of hospitals had physostigmine available, and the authors suggested that all hospitals should have it as part of their emergency preparedness (6).

«Treatment with physostigmine should be considered if delirium and sedation occur following injection of olanzapine»

Drugs with anticholinergic effects

Many major drug groups have anticholinergic properties that are easily forgotten because the drugs are marketed under other primary labels. Examples include psychotropic drugs, antihistamines, anticholinergic antiparkinson agents, certain antiarrhythmics, certain opioids and certain antiemetic agents (1, 7). Concomitant use of several drugs from these groups can therefore result in the total anticholinergic effect becoming significant. In the elderly, this can lead to problems with activities of daily living (8). The anticholinergic effect can be particularly pronounced in the event of overdoses, either accidentally or with suicidal intent. In such circumstances, the use of physostigmine can reverse most of the symptoms almost immediately, and a rapid effect of physostigmine therefore contributes to a diagnosis of central anticholinergic syndrome (1).

Compared with other atypical antipsychotics, olanzapine and clozapine have a particularly high affinity for muscarinic acetylcholine receptors (7, 9, 10). Oral intake of large quantities of olanzapine has been reported to give rise to a condition consistent with central anticholinergic syndrome (11). The use of physostigmine reversed the symptoms almost completely and thereby demonstrated that the blockade of muscarinic acetylcholine receptors was involved. Even though only two cases were described in this report, it is clear that the idea that a high dose of olanzapine has a physostigmine-sensitive central anticholinergic effect must be considered sound.

Oral overdoses of olanzapine taken with suicidal intent have been reported previously (12, 13). Both reports refer to «anticholinergic symptoms», but neither of them mentions the possibility of investigating whether the condition is physostigmine-sensitive (12, 13).

Post-injection syndrome upon use of olanzapine

Olanzapine is available as a long-acting preparation for intramuscular injection. For a number of patients it is definitely advantageous to be given the drug in this form; for example, to increase treatment compliance. Every relapse is regarded as unfortunate and detrimental with regards to the aim of achieving full remission (14, 15). In < 0.1 % of injections and in approximately 2 % of patients who have olanzapine administered in this way (16), a post-injection syndrome has been described that in some cases begins almost as soon as the injection has been completed (17, 18). This phenomenon is called post-injection delirium/sedation syndrome (PDSS). The symptomatology is consistent with an olanzapine overdose (e.g., sedation, confusion,

slurred speech, altered gait, unconsciousness). One study concluded that in spite of proper injection technique, injected olanzapine can occasionally leak into a vein, perhaps as a result of damage to the vessel wall caused by the injection, and lead to a very high serum concentration of olanzapine, giving rise to the aforementioned syndrome (19).

Post-injection syndrome occurs after injection of olanzapine, but not after injection of risperidone or paliperidone (20). This is consistent with the fact that risperidone and paliperidone have very low affinities for muscarinic acetylcholine receptors compared with olanzapine (7). In two comprehensive review articles, the possibility that post-injection syndrome could be at least in part consistent with a central anticholinergic syndrome was not even mentioned (15, 20). Neither of these papers refers to the study that used and demonstrated an effect of physostigmine in two patients (11), but they instead conclude that there is no specific antidote to olanzapine. It is correct that there is no specific antidote to olanzapine *per se*, but there is an antidote to the component of its effect that is due to muscarinic acetylcholine receptor blockade: physostigmine. In our view, history has repeated itself yet again. «The forgotten diagnosis» must once again be recalled, for there is no label on olanzapine to indicate that it has anticholinergic properties.

Physostigmine as part of emergency preparedness

Physostigmine should be available among antidotes in line with flumazenil and naloxone. However, physostigmine does strengthen the effects of endogenous acetylcholine, something one must be aware of if it is to be used safely (1, 2). It should therefore be handled by anaesthesiologists/medical personnel with sufficient knowledge and expertise. The long-acting injectable form of olanzapine should be administered by trained personnel who are aware of the possibility of a post-injection syndrome with central anticholinergic effects.

We believe that patients must be observed for at least three hours following injection of olanzapine. Where olanzapine is administered at institutions without anaesthesiology personnel in the immediate vicinity, those who administer the drug intramuscularly must summon help should post-injection syndrome arise. Physostigmine can then be administered by the ambulance service, perhaps in consultation with the local emergency response centre. Physostigmine is not included in the ambulance service's arsenal of drugs at the present time (Anders Holtan, personal communication, 2012). We recommend that physostigmine should be available in those places where intramuscular injections of olanzapine are performed.

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Received 15 March 2013, first revision submitted 7 June 2013, approved 8 October 2013. Editor Kristin Viste.