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Accidental subarachnoid injection of atracurium: A case report

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Introduction

Spinal anesthesia is a common method and is applied for a variety of surgical procedures. However, spinal anesthesia may be associated with the potential hazard that the wrong drugs may, accidentally, be administered into the subarachnoid space.

Although the pharmacological effects of neuromuscular blocking (NMB) drugs in the cerebrospinal fluid (CSF) are unknown in humans, several observations suggest that NMB drugs are not inert when they have been injected into the CSF [1].

The present report describes a patient who developed weakness and generalized muscle hypotonia, tachycardia, hypotension, diplopia, and felt general discomfort after the accidental subarachnoid injection of atracurium.

Case report

A 22-year-old man, weighing 70 kg, was scheduled for hemorrhoidectomy. Clinical and biochemichical tests showed normal values. We decided to use spinal anesthesia for his operation. Before spinal anesthesia, 0.03 mg·kg^{-1} midazolam was given intravenously (IV) and 500 ml crystalloid fluid was administered. Electrocardiogram (ECG), mean arterial pressure (MAP), heart rate (HR), and arterial hemoglobin oxygen saturation (SpO_2) were measured with a Millenia device (Millenia, Orlando, FL, USA). MAP and HR were 80 mmHg and 72 beat·min^{-1}, respectively. A lumbar puncture was performed with the patient in the left lateral position. Under local anesthesia, a 22-gauge spinal needle was placed in the subarachnoid space at the L2–3 interspace, using a median approach. Its position was confirmed by the appearance of CSF oozing through the needle.

When the anesthetist performing the block needed to fill the syringe being used, the nurse, by mistake, passed him an ampule containing 5 ml (50 mg) of atracurium, instead of hyperbaric 1% bupivacaine solution. The content of the ampule was aspirated into the syringe and then 3 ml fluid was injected into the subarachnoid space.

The patient was placed in the supine position with a pillow under his shoulders and head. This technique usually produces analgesia up to the T8–10 dermatomes. At this stage, the patient complained of diplopia and blurred vision, and then a general feeling of discomfort. Hypotension and tachycardia occurred. MAP and HR were 40 mmHg and 130 beat·min^{-1}, respectively. All of these changes occurred after the administration of the drug into the subarachnoid space. Intravenous crystalloid infusion was restarted as soon as possible. Two minutes after the subarachnoid administration of the drug, MAP and HR were normalized, and the patient's feeling of discomfort had disappeared. MAP and HR were 75 mmHg and 80 beat·min^{-1}, respectively. The patient continued to complain of diplopia and blurred vision. When an assessment of the level of analgesia to the pinprick test was made 5 min later, it was apparent that there was no analgesia. At the same time, the patient showed progressive and generalized muscle hypotonia.

When the sudden hemodynamic occurred changes, SpO_2 dropped to 94%. We started oxygen administration with a mask. Then, SpO_2 was elevated to 100%.

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The fact that 30 mg of atracurium had been administered instead of hyperbaric 1% bupivacaine solution was noticed at this point, when the empty ampule was discovered.

The patient's neuromuscular transmission was monitored with a Train of Four (TOF) guard device. When we applied a TOF stimulus, we found the TOF ratio to be 50% at the adductor pollicis muscle. The patient's ability to breathe, to open and close his eyes, to protrude his tongue, and to swallow was not affected. Values for handgrip test and head-lift test were moderately diminished.

It was then decided not to reverse the neuromuscular blockade. We decided to wait for the neuromuscular blocking effect to subside spontaneously. A skin temperature probe was placed, and heat loss was prevented. The diplopia was attenuated 20 min after the accidental injection of atracurium. Forty minutes after the accidental injection of atracurium, the TOF response was restored to 100%. After approximately 1 h, vision was determined to be perfect. The operation was cancelled, and a neurological examination was performed. Sensory, motor, and reflex findings were normal. Neurological examinations were performed again 1 week and 1 month later, and results proved to be normal. Hemorrhoidectomy was then performed successfully, with the patient under general anesthesia.

Discussion

There are several reports of the accidental injection of NMB agents into the subarachnoid space, but the acute or chronic sequelae of subarachnoid NMB injection are not clearly understood. NMBs may activate, rather than inhibit, particular subtypes of nicotinic acetylcholine receptors found in the central nervous system (CNS). This paradoxical effect may be the result of the substantial differences in subunit composition and pharmacology between central and neuromuscular nicotinic acetylcholine receptors. One important difference between these central and neuromuscular receptors is that the predominant brain subtype of nicotinic acetylcholine receptors, which consists of alfa-4 and beta-2 subunits, is seven times as permeable to calcium as the neuromuscular junction receptor. NMBs also interact with brain muscarinic acetylcholine receptors. For example, pancuronium appears to activate brain muscarinic receptors, because atropine inhibits the increase in calcium caused by this agent. It is possible that a given concentration of NMB could act simultaneously as an antagonist and an agonist in different subtypes of acetylcholine receptors, or in different brain regions expressing different subsets of receptors. It is clear that acetylcholine receptors are present on both pre and postsynaptic membranes, as well as on non-neuronal cells within the CNS [2].

Nondepolarizing NMB drugs are highly ionised. They have relatively low lipophilicity and normally do not cross the blood-brain barrier [1]. When an NMB is administered intravenously in humans, a small quantity can be detectable in CSF [3]. In humans, accidental injection of small doses of gallamine or pancuronium into CSF has been reported to cause autonomic dysfunction and/or weakness [4–6]. Although our patient recovered with no neurological sequelae, there is both clinical and experimental evidence that convulsions and neuronal death ensue when NMB agents such as gallamine or tubocurarine are directly applied to the brain or accidentally injected into the lumbar CSF [7–10]. NMB causes excitement and seizures when introduced into the CNS [2,11]. In rats it was reported that acute intrathecal administration of NMB acted peripherally as a nicotinic receptor antagonist, leading to a dose-dependent CNS effect, culminateing in seizures [1]. The increase in Ca^{+2} induced by NMB drugs may be relevant to the mechanism by which these drugs induce seizures [1]. Atracurium has a special feature in that laudanosine, its metabolite, may contribute to seizure activity, when atracurium is given intravenously. Our patient had general discomfort, but no seizure was observed. Our patient's first sign after the accidental injection of atracurium was the disturbance of vision such as blurring and diplopia.

Anesthetic agents generally disappear from the subarachnoid space through the arachnoid villi, and directly into the capillary or lymphatic channels of nerve bundles, or into capillaries of nerve tissue parenchyma. It has been determined that the greater portion of the drug leaves the subarachnoid space through venous drainage. The rate of elimination of agents injected into the subarachnoid space is regulated by diffusion [12]. The epidural space is rich in venous plexuses. Drugs administered into the epidural space are exposed to a large vascular surface. The absorption of local anesthetics from the peridural space occurs in a biphasic manner. The initial phase is characterized by short, rapidly reached high peak plasma times. As the peak levels decline, there is a slower, second phase, of absorption, lasting for up to 3–7 h [13]. These differences between subarachnoid and epidural injections could be helpful for the understanding of their pharmacokinetics.

Several studies suggest that NMB agents introduced into the CNS are pharmacologically active. Autonomic dysfunction, weakness, neuromuscular blockade, neuronal death, and seizures have been observed [2]. In our patient, we observed general discomfort, blurred vision, and diplopia, and transient hemodynamic changes. These observations may be associated with the autonomic dysfunction caused by NMBs when they are in-

jected into the subarachnoid space. Atracurium has a molecular weight of 1243, with a low pH and plasma half-life of 20 min. Transient, severe hypotension is unlikely to be caused by systemic histamine release secondary to systemic absorption from the subarachnoid space. The brain and spinal cord have a complex structure, with different receptor concentrations, and atracurium causes strong histamine releasing actions. So we think that histamine release caused by atracurium administration into the CSF may have been responsible for the hemodynamic changes in our patient. Hemodynamic changes such as hypotension and tachycardia occurred only in a period of 2 min. At first, we thought this was due to the sympathetic block of spinal anesthesia. However, when we discovered that the wrong injection had been given, we thought that the hemodynamic changes were caused by direct histamine-releasing actions of the intrathecally injected atracurium. The duration of the hemodynamic change was short. As a matter of fact, histamine has a short duration of action, and this supports our idea. There is some absorption of atracurium from the CSF into the systemic circulation, and this produces muscle weakness. Hemodynamic changes in our patient were observed shortly after the inadvertent injection of atracurium, but the neuromuscular abnormality lasted for longer. Peduto et al. [6] claimed that the intrathecal injection of hyperbaric 1% bupivacaine solution a few minutes after the accidental injection of an NMB into the subarachnoid space may help in limiting the diffusion of the NMB out of the lumbar area. We thought that this injection may be harmful, because the long stay of an NMB in the CSF may prolong the neural effects. The degradation of atracurium by Hoffman elimination, pH effects, and heat are very important in the pharmaco kinetics. Prevention of a fall in body temperature may be helpful in atracurium degradation. Warming with a blanket was thought to be helpful for the degradation of atracurium.

An accidental spinal injection of atracurium in this patient was, fortunately, devoid of neurological sequelae. This case demonstrates that there is some absorption of atracurium from the CSF into the systemic circulation, resulting in prolonged partial blockade of neuromuscular conduction.

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