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Research Article

Excessive sweating following intrathecal μ agonists: Effective atropine management

Alaa Mazy *,[1]

Mansoura Faculty of Medicine, Mansoura University, Egypt

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Abstract Many thermal distortions may accompany the profound extended analgesia of intrathecal μ agonists. Hypothermia is the commonest, but a syndrome including a profuse sweating was also reported. Conservative management for this sweating extends patient suffering more than 6 h. Other treatment options showed variable success rates. In a case series, atropine sulfate showed effective sweat suppression following intrathecal morphine 0.3 mg or fentanyl 25 mcg. Treatment options and possible mechanisms of sweating are reviewed in relation to opioids, regional block and general patient factors.

1. Introduction

Hypothermia, commonly associates the analgesia of intrathecal (IT) μ agonist opioids [1]. In addition, a profuse sweating sometimes appears within a syndrome that starts about three hours of injection, also comprising, feeling hotness, lethargy, itching, nausea, vomiting, hypothermia without shivering and sometimes dysphoria [2–8]. However, patients are hemodynamically stable with normal electrolytes, complete blood count, ECG, troponin, serum cortisol and thyroid stimulating hormone and not responding to aggressive warming measures [3,7].

The mechanism of this syndrome is not clear. Active treatment options included naloxone [3] and lorazepam [4,6,7]. Atropine is suggested as an option in this study.

1.1. Thermal effects of anesthesia

General [9] and regional anesthesia [10], as well as IT opioids [11] highly increased the thermostatic inter-threshold range thus intensifying hypothermia [12]. Opioids inhibit the warm-sensitive neurons in the medial preoptic area of the hypothalamus which is the principle center for thermoregulation [13]. IT morphine (Mo) can reach the opioid receptors in the hypothalamus through cephalad spread within CSF causing new setting of thermoregulatory center that the inter-threshold range was above this new upper temperature threshold generating sweating [5]. Nevertheless, opioids exert a range of thermoregulatory effects, depending upon various factors, such as animal species, age, circadian rhythms, route of administration and dose [14].

2. Case series and results

The first case involved in this study (Table 1, case1) managed conservatively only, due to lack of experience with this phenomenon. Knowledge regards this syndrome stimulated

* Address: Mansoura Faculty of Medicine, Mansoura University, Egypt. Tel.: +20 1140065052.
[1] Associate professor of anesthesia and surgical intensive care.

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Table 1 Clinical, surgical and anesthetic data of case1 – conservatively treated.

Patient Age/sex	Medical problems	Surgery/duration	IT drugs	Symptoms & signs	Onset after spinal	Treatment	Treatment efficacy
Case 1 59 y/f	DM, HTN, IHD, LBBB AF	Total knee arthroplasty/3.5 h	20 mg Bup +0.3 mg Mo	Hypotension	10 min	Ephedrine (total 20 mg)	(+)
				Itching	30 min	Diphenhydamine 45.5 mg	(−)
				Sweating, hotness, weakness, BP 130/80, HR 70/min 35.8 °C	2.5 h	Conservative	(−) (Sweating for 12 h)
				Hypoglycemia (RBS 75 mg)	2.5 h	5% dextrose (Still sweating)	(+) (RBS 175 mg)
				N&V	2.5 h	Metoclopramide, granisetron	(±)

F: female, y: years, DM: diabetes mellitus, HTN: hypertension, IHD: ischemic heart disease, LBBB: left bundle branch block, AF: atrial fibrillation, h: hours, IT: intratheal, Bup: Bupivacaine, Mo: Morphine, RBS: random blood sugar, N&V: Nausea & vomiting. Treatment Efficacy for controlling the symptoms: (+) Effective, (−) not effective, (±) partial control.

prospective search about further cases for trial evaluation of atropine as a treatment for this sweating. Over two years (2014–2015) observation attained more three cases (Table 2, cases 2, 3, 4) among 217 consecutive patients underwent lower limb orthopedic surgery under spinal anesthesia using IT: 15–20 mg 0.5% heavy bupivacaine plus Mo 0.2–0.3 mg in 32% of patients, or fentanyl 25 micrograms (mcg) in 68% of patients. Mean age was 34 years (range: 17–72). Results revealed that the incidence of the profuse sweating syndrome in these patients was 1.8%. Sweating started about three hours after spinal injection. This syndrome was detected intra operatively in all cases except case 4 (Table 2) that was consulted six hours postoperatively due to profuse sweating, vomiting and urine retention. Atropine was tried in the last 3 cases as 0.5 mg increments. Atropine 1 mg was promptly effective within minutes in discontinuing this sweating without recurrence. Subsequently temperature was rising slowly. Tables 1 and 2 display the clinical, surgical and anesthetic data of these cases.

3. Discussion

This study showed that atropine controlled the sweating following IT Mo or fentanyl. The incidence of the excessive sweating in this study was 1.8%. Erdine et al. reported the same rate of sweating after IT morphine [15]. Hess et al. reported an incidence about 7% [4], the same as Paice et al. [16]. This rate may be up to 9% with both transdermal fentanyl and oral Mo [17] and up to 40% in patients on long-term methadone treatment [18]. The treatment options and possible etiologies will be discussed.

3.1. First: Treatment options

3.1.1. Atropine

Atropine effectively controlled the profuse sweating following IT Mo or fentanyl in this study. The nerve supply of sweat glands is mainly cholinergic [19] with a few adrenergic terminals [20]. Acetylcholine is the main pre and postganglionic transmitter of the sympathetic nervous supply of the sweat glands [21], and hence the rationale of using atropine as an anticholinergic greatly attenuates or abolishes sweating [22]. Atropine suppressed thermal and non-thermal sweating where both types are cholinergic [23]. The cholinergic system is also involved in Mo-induced hyperthermia [24].

Similarly, the anticholinergic hyoscine controlled the opioids – induced sweating [25]. On the contrary, IT neostigmine 100 mcg, produced profuse sweating, agitation, nausea and vomiting [26].

Atropine has the advantage of high end-organ efficacy whatever the mechanism of sweating. The tachycardia combining atropine may be beneficial against the high degree of cardiac vagal activity associated spinal anesthesia [27] or the parasympathetic predominance associated Mo as confirmed by heart rate variability [28].

3.1.2. Naloxone

Thermal changes of μ agonists are opioid receptor effects. Naloxone antagonized sweating, hypothermia, sedation, pruritus, nausea and vomiting [29,30]. On the other hand, naloxone

Table 2 Clinical, surgical and anesthetic data of atropine treated cases.

Patient Age/sex	Medical problems	Surgery/duration	IT drugs	Symptoms & signs	Onset after spinal	Treatment	Treatment efficacy
Case 2	No	Illizarov for fracture tibia/5 h	20 mg Bup	Mild Itching	30 min		
28 y/m			+25 mcg fentanyl	Sweating, drowsiness, BP 110/65, HR 80/min RBS 176 mg	2.5 h	Atropine 1 mg	(+)
				Vomiting	2 h	Propofol 30 mg	(+)
Case 3	HTN	Knee arthroplasty/3.33 h	20 mg Bup	Sweating, N&V,	2.7 h	Atropine 1 mg Metoclopramide 10 mg	(+) (+)
50 y/f			+0.3 mg Mo	Weakness, Drowsiness			
Case 4	No	Ankle arthroscopy/1.5 h	15 mg Bup	Hypothermia (35.5 °C)	2 h	Conventional rewarming	(−)
32 y/m			+0.2 mg Mo	Sweating, consulted after 6 h BP 110/70, HR 88/min, RR 17/min	3.5 h	Atropine 1 mg	(+)
				Vomiting (4 times)	3.5 h	Granisetrone 1 mg	(+)
				Urine retention	4 h	Catheterization	(+)

F: female, m: male, y: years, h: hours, HTN: hypertension, Bup: Bupivacaine, Mo: Morphine, RBS: random blood sugar, N&V: Nausea & vomiting. Treatment Efficacy for controlling the symptoms: (+) Effective, (−) not effective, (±) partial control.

utilization was associated with excessive shivering [3], and it has a short duration of action [31].

3.1.3. Lorazepam

Lorazepam attenuated the thermal changes of IT opioids [4,7]. Benzodiazepines inhibit the inhibitor neurons in the preoptic area of the anterior hypothalamus, releasing the dorsomedial area of the hypothalamus, leading to activation of effector neurons to increase body temperature [32]. Experimentally, GABA-enhancing drugs attenuated Mo-induced hyperthermia [33]. But lorazepam partially (80%) controlled the sweating and hypothermia [4].

Actually the previous three treatment modalities are not contradictory, where several neurotransmitters such as acetylcholine, serotonin, GABA and opioids are involved in thermoregulation [34].

3.1.4. Other drugs

Generally, nonsteroidal anti-inflammatory agents and steroids have no clear benefit to control this sweating [25].

Antihistamines showed a possible benefit in two similar patients [35]. Moreover, some antihistamines as diphenhydramine can exhibit anticholinergic action [36].

Catecholamines augment sweating [37], but in a weaker rate than the one triggered by cholinergic stimulation [38]. Antiadrenergic drugs are supposed to be effective especially in adrenergic mediated emotive sweating that is stimulated by stress, anxiety, fear and pain. But β blockers are not effective in treating sweating [39]. Ephedrine has a negligible contribution to sweating [38]. An exception to this rule was in patients with complex regional pain syndrome, in whom increased α-receptor sensitivity augments sweating [40]. This syndrome can be precipitated by arthroscopic procedures of the knee as a common cause [41].

3.2. Second: Possible etiologies of sweating

The mechanism of this sweating is not clear, but opioids are mainly incriminated [2,3,5,7]. The cause of delayed onset and why only few patients – not all – given IT μ agonists display this syndrome is not clear? So there may be an additional contributing factors related to the opioids, regional anesthesia or patient general factors.

The delayed onset was explained as the time elapsed until cephalad spread of Mo to the hypothalamic opioid receptors [3,5]. Although this well not explains why not all patients given IT opioids develop this syndrome? In particular there is no correlation to the dose, where this syndrome appeared after either small dose (50 mcg) [42], or large dose (4 mg) [6]. There is also a possibility that IT Mo acts directly on the spinal cord generating these thermal effects [43].

The delay may correlate with the accumulation of the metabolite morphine-3-glucuronide (M3G). The maximum concentration of M3G in the CSF is three hours after intracerebroventricular injection of morphine [44]. Moreover, M3G produces the excitatory side effects of morphine [45] that may explain the associated nausea, vomiting and itching [46].

Accumulation of serotonin may be a reason. Its level increases 50% after Mo administration [47]. That occurs through the opioid-mediated inhibition of GABA presynaptic inhibitory effect on serotonin release [48]. Also serotonin is increased by its reuptake inhibition with other piperidine opioids such as fentanyl [49]. Co-administration of opioids with other serotonergic drugs can precipitate serotonin syndrome. These drugs are commonly used perioperatively, such as metoclopramide, ondansetron, granisetron, chlorpheniramine, ginseng, dextromethorphan and antidepressants for neuropathic pain [50]. Serotonin syndrome is characterized by a triad of mental state and neuromuscular tone alteration, plus autonomic hyperactivity that can appear as diaphoresis without fever [49].

Experimentally, IT Mo has a biphasic thermal pattern. That high doses produce hypothermia by κ-opioid receptors stimulation [51], while the low doses produce hyperthermia by μ-opioid receptors activation, increasing thermoregulatory set point, oxygen consumption and peripheral vasoconstriction [52]. This hyperthermia is maximum at 2–3 h after subcutaneous morphine in rats [53]. But hyperthermia may appear only in the presence of high ambient temperature [54]. The profuse sweating in patients is associated with hypothermia, proposing a central distortion by opioids rather than a thermoregulatory response [5].

The duration of thermal effects of IT morphine ranges from 6–7 h [4,7] to 22 h [2]. Regardless of the short duration of action of fentanyl, its IT analgesia extends about five hours [55].

Regional anesthesia may contribute to sweating through triple factors: vasodilatation, blocked cold sensation and apparently elevated leg temperature [56]. The brain interprets this as a warming that results in heat loss. Fever without infection may occur in association with regional block especially during labor [57] and post-operatively [58], where sweating is reduced in the blocked area, therefore passive hyperthermia is induced if heat production exceeds heat loss. But we can exclude these effects as sweating is associated with hypothermia and it follows opioids and not bupivacaine alone.

None of the general factors such as patient characteristics, operative procedure, intraoperative fluid administration, or estimated blood loss was conclusive for anticipating the occurrence of sweating [2,3,5,7]. In addition many non-thermal factors can affect the central [59] and peripheral heat sensors [60].

The hypothalamus responds not only to changes in core temperature but also to hormones, physical activity, endogenous pyrogens and emotions [59].

Transient receptor potential (TRP) is the principal temperature sensor [61]. The hot-activated receptors are non-selective channels. They are gated by specific range of temperature, as well as adenosine triphosphate and protons, also sensitized directly by inflammatory mediators including growth factors, peptides, lipids, neurotransmitters, chemokines and cytokines and indirectly by binding to metabotropic receptors [60]. Mo inhibits the cold receptor TRPM8 (M: melastatin) [62] and TRPV1 (V: vanilloid) warm receptors [63].

Hypovolemia impairs sweating [64], but decreased preload can cause more than reflex bradycardia as demonstrated by progressive vagal symptoms including sweating, nausea and syncope [65]. Conversely, hypervolemia does not contribute to sweating [66].

The profuse sweating may contribute to fluid and electrolyte imbalance, besides considerable energy loss [39]. Also it aggravates hypothermia which is already resistant to re warming [7].

4. Limitations of this study

This is an observational prospective study, reporting the efficacy of atropine treatment in spite of low patient's number. The low incidence, lake of awareness and unfeasible anticipation of associations of this phenomenon add difficulties in etiological determination. The site of atropine action is not defined whether it is peripheral on sweat glands or central on cholinergic pathways. Perioperative records of patients and room temperatures were not complete.

5. Conclusion

Atropine effectively controlled the excessive sweating associated IT Mo or fentanyl administration in this case series. Further randomized studies are recommended to confirm this effect. The sweating mechanism is not clear. Opioids' central thermal, cholinergic and serotonergic effects may be incriminated. Awareness regards opioids thermal distortions deserve attention.

Conflict of Interest

The author declare that there are no conflict of interest.

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