Dexmedetomidine-associated hyperthermia

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Introduction

Dexmedetomidine hydrochloride is a potent, highly selective alpha-2 adrenergic receptor agonist. It is mostly used for sedation in the intensive care unit (ICU).

In our institution, certain patients on dexmedetomidine developed high temperatures without a clear alternative cause, particularly following open heart surgery (OHS) and in those with an elevated body mass index (BMI). This led us to suspect drug fever. For the purposes of this study we chose a temperature threshold of ≥39.5°C to amplify any potential association between dexmedetomidine and hyperthermia.

The dexmedetomidine product literature lists pyrexia as a side-effect with a greater incidence (7.4%) compared with midazolam (2.5%). In the MIDEX trial, hyperthermia was more common in the dexmedetomidine arm, with an incidence of 3.2% versus 0.8% (*P*=0.062) with midazolam. In the PRODEX trial, the incidence of hyperthermia was 0.8% with dexmedetomidine compared to 0% with propofol. Although other alpha-2 adrenergic receptor agonists such as methyldopa, methylenedioxymethamphetamine (MDMA) and clonidine are known to cause drug-related hyperthermia, dexmedetomidine-associated hyperthermia has only been the subject of rare case reports in the literature.

Sixty cases (10% of all adverse events) reported to the FDA regarding dexmedetomidine are related to the occurrence of hyperthermia and include pyrexia, chills, neuroleptic malignant syndrome (NMS), hyperthermia, rhabdomyolysis, malignant hyperthermia, postoperative fever, multi-organ failure or sepsis. Despite these reports, clinician awareness of dexmedetomidine-associated hyperthemia remains low and recent dexmedetomidine reviews do not report hyperthermia as a potential adverse drug reaction.

Aim

Review the association between dexmedetomidine use and hyperthermia in ICU patients.

Methods

All ICU admissions over a seven year period were included, except for patients with missing temperature data.

Patient characteristics included age, gender, Acute Physiology and Chronic Health Evaluation (APACHE) II score, invasive ventilation, renal replacement therapy (RRT), usage of dexmedetomidine, noradrenaline, neuroleptics, antidepressants and antibiotics (meropenem, vancomycin, piperacillin-tazobactam) during the ICU admission, Elixhauser comorbidities, APACHE III coded sepsis, proven infection whilst in ICU and BMI >35 kg/m^2.

Hourly temperature recordings were extracted and the maximum temperature was determined during each admission. Temperatures ≥39.5°C were selected and examined for their association with death. Those exposed to dexmedetomidine had their temporal temperature data extracted, including baseline temperature at the commencement of the infusion and the highest temperature recorded in the subsequent 24 and 48 hours. The mean delta difference was determined for all patients and a subanalysis of patients with obesity (BMI >35 kg/m^2) or admission post–OHS was also performed.

Univariate and multivariate analyses were performed for exposure to dexmedetomidine and reported temperatures ≥39.5°C. Confounders included in the multivariate model were chosen based on common attributable causes of temperature elevations within the critically ill population.

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Results

There were 9,931 individual ICU admissions between 1 July 2009 and 31 May 2016. Temperature records were available for 9,782 admissions (98.5%), of which 341 (3.5%) had temperatures ≥ 39.5°C.

Dexmedetomidine was administered in 611 admissions (6.3%) (Figure 1). Relevant patient demographics are shown in Table 1.

In the study cohort, overall hospital mortality was 10.8% compared to 29.3% in the subgroup with temperatures ≥39.5°C.

Multivariate analysis (Table 2) was performed in 9,651 cases (131 exclusions due to missing data). Receipt of dexmedetomidine remained significantly associated with a temperature ≥39.5°C after adjustment for possible causes of high temperatures or differences in patient characteristics (OR 1.61; 95% CI 1.1, 2.3; *P* <0.01).

The temporal relationship between dexmedetomidine and elevated temperature was studied in 610 cases (Figure 2, 3 & 4). Across the cohort, the mean temperature at the initiation of dexmedetomidine was 37.17°C (SD 0.76). At 24 hours, the mean highest recorded temperature was 37.76°C (SD 0.85), i.e. a mean increase from baseline of 0.59°C (95% CI 0.5 to 0.68; *P* <0.001). At 48 hours, the mean highest recorded temperature was 37.95°C (SD 0.86), i.e. a mean increase from baseline of 0.78°C (95% CI 0.69 to 0.88), *P* <0.001. For OHS patients with a BMI >35 kg/m^2 (n = 32), the mean temperature increase at 24 hours and 48 hours was 0.7°C (95% CI 0.3 to 1.1), *P* <0.001 and 0.91°C (0.45 to 1.36), *P*<0.001 respectively.

***Figure 1**: Study flow chart*

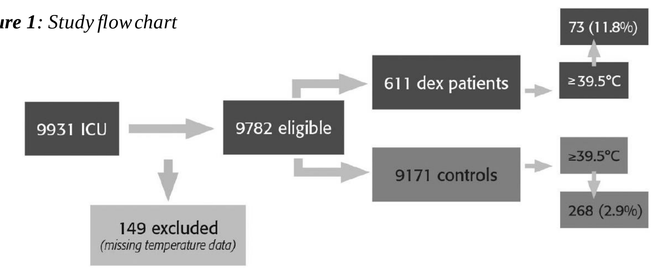


***Table 1**: Patient characteristics and univariate analysis*

Patient characteristic	All	Exposed	Unexposed	*P*-value
n	9,782	611	9,171	
Mean age, years (SD)	61.8 (16.3)	55.8 (16)	61.7 (16.3)	<0.001
Male gender	6,239 (63.8%)	456 (74.6%)	5,783 (63.1%)	<0.001
Elixhauser comorbidities (IQR)	3 (2–4)	3 (2–4)	3 (2–4)	<0.001
Temperature ≥39.5°C	341 (3.5%)	73 (12%)	268 (2.9%)	<0.001
Admission from theatre	5,222 (53.4%)	242 (39.6%)	4,980 (54.3%)	<0.001
OHS admission	2,912 (29.8%)	162 (26.5%)	2,750 (30.0%)	0.07
OHS admission ≥39.5°C	24 (0.8%)	10 (6.2%)	14 (0.5%)	<0.001
BMI >35 kg/m^2	729 (12.8%)	94 (17.8%)	635 (12.3%)	<0.001
Mean APACHE II Score (SD)	16.3 (6.7)	17.3 (6.0)	16.2 (6.7)	<0.001
Ventilated	6,305 (64.5%)	559 (91.5%)	5,746 (62.7%)	<0.001
Noradrenaline	4,727 (48.3%)	439 (71.9%)	4,288 (46.8%)	<0.001
RRT	643 (6.6%)	88 (14.4%)	555 (6.1%)	<0.001
Sepsis: APACHE III diagnosis	723 (7.4%)	52 (8.5%)	671 (7.3%)	0.28
Proven infection	3,188 (32.6%)	364 (59.6%)	2,824 (30.8%)	<0.001
Vancomycin/meropenem/piperacillin-tazobactam	3,206 (32.8%)	343 (56.1%)	2,863 (31.2%)	<0.001
Neurological diagnosis	618 (6.3%)	56 (9.2%)	562 (6.1%)	<0.003
Antidepressants	467 (4.8%)	37 (6.1%)	430 (4.7%)	0.13
Use of neuroleptics	1,039 (10.6%)	281 (46.0%)	758 (8.3%)	<0.001
Died during ICU stay	702 (7.2%)	43 (7.0%)	659 (7.2%)	0.89
Died during hospital admission	1,065 (10.9%)	58 (9.5%)	1,007 (11.0%)	0.25

***Table 2**: Multivariate analysis between temperature ≥39.5°C and potential confounders in all patients (n=9,651) and in those with available BMI data (n=5,633)*

	All patients			Patients with BMI data		
Variable	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Dexmedetomidine	1.61	1.1–2.3	<0.01	1.14	0.8–1.7	0.539
Obesity (BMI >35 kg/m^2)	–	–	–	0.67	0.4–1.1	0.133
Dexmedetomidine and obesity	–	–	–	3.44	1.5–7.9	0.004
OHS admission	0.30	0.2–0.6	<0.001	0.21	0.1–0.4	<0.001
Dexmedetomidine and OHS	2.72	1.1–6.9	0.035	3.46	1.3–9.0	0.011
Mean age, years	0.97	0.96–0.98	<0.001	0.97	0.96–0.98	<0.001
Male gender	1.28	0.99–1.7	0.061	1.20	0.9–1.6	0.227
Elixhauser comorbidities	1.01	0.9–1.1	0.714	1.04	0.96–1.1	0.347
Admission from theatre	0.88	0.6–1.2	0.438	0.93	0.6–1.3	0.689
Mean APACHE II score	1.04	1.0–1.1	<0.001	1.03	1.0–1.1	0.006
Ventilated	2.25	1.6–3.2	<0.001	3.35	2.0–6.1	<0.001
Noradrenaline	1.73	1.3–2.4	<0.001	1.30	0.9–1.9	0.149
Sepsis: APACHE III diagnosis	1.49	1.1–2.1	0.022	1.73	1.2–2.6	0.008
Proven infection	2.44	1.8–3.4	<0.001	2.13	1.5–3.1	<0.001
Piperacillin-tazobactam	1.83	1.4–2.4	<0.001	1.90	1.4–2.6	<0.001
Vancomycin/meropenem	3.44	2.6–4.6	<0.001	2.96	2.1–4.1	<0.001
Neurological diagnosis	4.01	2.9–5.6	<0.001	4.06	2.8–5.9	<0.001
RRT	0.59	0.4–0.9	0.006	0.60	0.4–0.9	0.016
Antidepressants	1.69	1.0–2.7	0.032	1.48	0.8–2.7	0.200
Neuroleptics	1.06	0.8–1.5	0.708	1.02	0.7–1.5	0.935

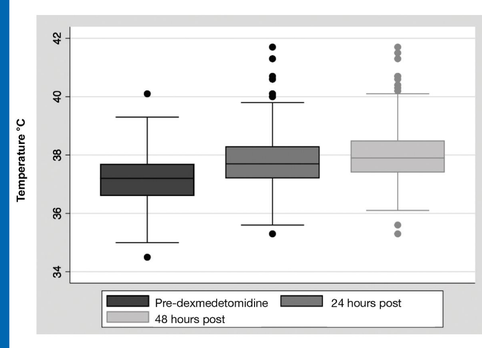


***Figure 2**: Box plot of temporal relationship between dexmedetomidine and recorded temperatures at baseline (drug initiation) and highest temperatures recorded within 24 and 48 hours post-initiation*

***Figure 3**: Scatter plot of temperatures before and after commencing dexmedetomidine (n=610)*

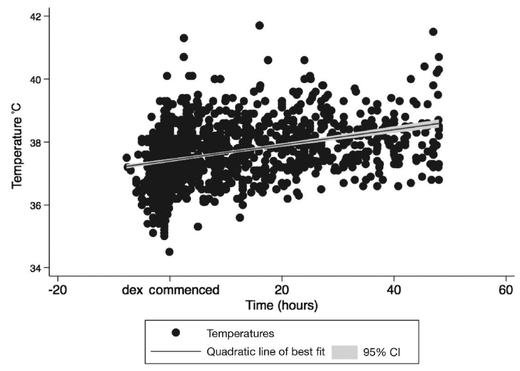
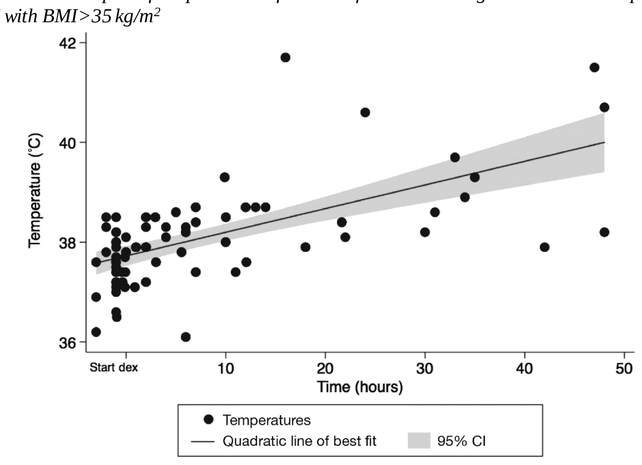


***Figure 4**: Scatter plot of temperature before and after commencing dexmedetomidine post-OHS with BMI>35 kg/m^2*



Discussion & Conclusion

This study shows a strong temporal association that dexmedetomidine is a risk factor for hyperthermia. The association appears stronger for patients post–OHS and those with obesity. Obesity and OHS were not associated with temperatures ≥39.5°C on their own; however, if exposed to dexmedetomidine, the odds increased at least threefold.

Adipose tissue is a secretory organ controlling energy homeostasis. Obesity is characterised by low-grade systemic inflammation and increased sympathetic activity. This pro-inflammatory state, in concert with other organ failures or triggers may put obese patients at risk of hyperthermic complications.

Overall, dexmedetomidine-associated hyperthermia mechanisms are likely to be multifactorial with both central and peripheral determining factors. The mechanism may conceivably be different in different patients. Alpha-2 agonists regulate release and function of monoamines and thus could alter body temperature regulation. Both clonidine and dexmedetomidine alter shivering thresholds by action at the central alpha-2A adrenergic receptors. In animal studies where alpha-2A adrenoceptors were knocked out, the hypothermic effect of dexmedetomidine was attenuated. Polymorphisms of the alpha-2A adrenergic receptors or drug interactions may be factors for developing hyperthermia. Alternatively, it may be an allergic or idiosyncratic reaction.

Dexmedetomidine use is independently associated with high temperatures in our intensive care cohort. We recommend considering cessation of dexmedetomidine in patients whose temperature is ≥39.5C. Vigilance, a high degree of clinical suspicion and aggressive temperature management may be required. Future research should be directed at establishing prevalence, mechanisms, risk factors and other precipitants for this rare, but likely harmful, adverse event.