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Dexmedetomidine-Associated Hyperthermia: A Series of 9 Cases and a Review of the Literature

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Dexmedetomidine-Associated Hyperthermia: A Series of 9 Cases and a Review of the Literature

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Dexmedetomidine, an α_2 -adrenergic agonist, can be used to perform mild to moderate sedation in critically ill patients. In this case series, 9 cardiovascular intensive care unit patients with hyperthermia during dexmedetomidine administration, suggestive of drug fever, are presented. Hyperthermia ($>38.5^\circ\text{C}$) occurred 6 (4–10) hours (median [interquartile range]) after dexmedetomidine initiation at a dose of 1.0 (0.8–1.3) $\mu\text{g}/\text{kg}/\text{h}$ and was resolved 3 (1–8) hours after discontinuation of dexmedetomidine. All patients were screened for infectious and noninfectious causes of hyperthermia, and the findings were analyzed by 2 adverse drug reaction (ADR) assessment methods—the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment and the Naranjo ADR scale. This resulted in a “probable” ADR in all 9 patients (WHO) and a “probable” and “possible” ADR in 1 and 8 patients (Naranjo), respectively. This case series supports published case reports, suggesting that dexmedetomidine administration may be associated with the occurrence of clinically relevant hyperthermia. The underlying mechanisms and risk factors are uncertain and require further research. (*Anesth Analg* 2017;125:1898–906)

Fever in critically ill patients may have various etiologies. It usually triggers a multimodal diagnostic workup.¹ Infectious disease should primarily be ruled out to preclude possible evolution to sepsis, multiple organ dysfunction, and eventual death.² However, any empirical antibiotic therapy and other interventions triggered by hyperthermia may potentially be harmful, if unjustified.¹ This is particularly true when an elevated body temperature is actually drug-induced.^{3,4}

Dexmedetomidine is a highly selective α_2 -adrenergic agonist used to perform mild to moderate sedation in critically ill patients.⁵ Febrile episodes have been attributed to dexmedetomidine administration in several case reports.^{6–11} Here, we present 9 patients in a cardiovascular intensive care unit (ICU) with the onset of hyperthermia $>38.5^\circ\text{C}$ during

dexmedetomidine administration. Our goal is to increase awareness and stimulate further research on this topic.

METHODS

Data collection from the electronic patient information system was approved by the Institutional Review Board (Kantonale Ethikkommission Zurich, BASEC-ID: PB_2016-00333) and the need for informed consent waived. Statistics are descriptive, and results are given as median (interquartile range) or numbers (percentage). Of 1918 patients, admitted to our ICU during 2013 and 2014 after cardiac or major vascular surgery, 200 (10.4%) patients were treated with dexmedetomidine. Nine (4.5%) of these patients were selected for this case series (convenience sample) because of the occurrence of hyperthermia $>38.5^\circ\text{C}$ during dexmedetomidine administration.

In our ICU, dexmedetomidine is used for long-term sedation, during weaning from mechanical ventilation, and for the treatment of hyperactive delirium. It is usually started at a dose of 0.7–1.0 $\mu\text{g}/\text{kg}/\text{h}$ and titrated up to 1.4 $\mu\text{g}/\text{kg}/\text{h}$, according to clinical needs.⁵ Dexmedetomidine is discontinued if (1) continuous sedation can be omitted or delirium has improved, (2) hemodynamic instability occurs (norepinephrine $>0.3 \mu\text{g}/\text{kg}/\text{min}$, atrioventricular block $\geq\text{II}^\circ$, or bradycardia $<55 \text{ bpm}$ in the absence of a pacemaker), or (3) drug fever is suspected. In our ICU, microbiological sampling is usually triggered by a rise of the body temperature $>38.5^\circ\text{C}$. An empirical antibiotic therapy is subsequently started if an infection is suspected or if organ functions deteriorate.

All patients were screened for potential infectious and noninfectious causes of hyperthermia.¹ The association between dexmedetomidine and hyperthermia was assessed by 2 different ADR algorithms: The World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment and the Naranjo ADR scale. A causality assessment by the

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All investigators met all 4 criteria for authorship according to the recommendations of the International Committee of Medical Journal Editors (ICMJE).

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WHO-UMC criteria is accomplished by comparison of the drug-effect relationship in question with a table of predefined statements and yields the following categorization: unclassifiable, unclassified, unlikely, possible, probable, and certain (<http://www.whoumc.org/Graphics/26649.pdf>). The Naranjo ADR scale is a questionnaire-based scoring system (0 to ≥ 9 points), grading a drug-effect relationship into the following categories: doubtful (0), possible (1–4), probable (5–8), and definite (≥ 9).¹² Two ADR assessment methods were applied because the level of causality has been reported to differ between different pharmacovigilance algorithms.^{13,14}

RESULTS

Nine patients (age 67 [64–72] years, 5 [56%] male) under consideration underwent cardiac surgery ($n = 8$) or major vascular surgery ($n = 1$). Cardiac surgery was performed with cardiopulmonary bypass in 7 (78%) patients. Table 1 indicates the patients' characteristics, details of dexmedetomidine administration, and the occurrence of hyperthermia. Dexmedetomidine was initiated on postoperative day 1 (1–4) for the treatment of delirium in 2 patients (patients 4 and 6) and for sedation in 7 patients. The commencement dose was 1.0 (0.6–1.0) $\mu\text{g}/\text{kg}/\text{h}$. Hyperthermia was detected after 6 (4–10) hours at a dexmedetomidine dose of 1.0 (0.8–1.3) $\mu\text{g}/\text{kg}/\text{h}$. The maximum body temperature of 39.0°C (38.8–39.2°C) was observed after 11 (6–29) hours at a dexmedetomidine dose of 1.0 (0.8–1.0) $\mu\text{g}/\text{kg}/\text{h}$. Hyperthermia was present during 34 (12–38) hours, while dexmedetomidine was administered during 26 (9–35) hours. In no patient did the administration of acetaminophen and/or metamizole or the insertion of an intravenous cooling device (patient 1) lower the body temperature $<38.5^\circ\text{C}$. After dexmedetomidine discontinuation, the body temperature declined $\leq 38.5^\circ\text{C}$ and $\leq 38.0^\circ\text{C}$ after 3 (1–8) and 4 (3–9) hours, respectively. The temporal relationship between dexmedetomidine administration and hyperthermia is depicted in the Figure. Dexmedetomidine was discontinued because of (a) assumed drug fever (patients 1, 8, and 9), (b) discontinuation of sedation (patients 2, 3, 4, and 5), (c) insufficient sedative effect (patient 7), and (d) occurrence of a convulsive status epilepticus (patient 6).

Two patients (patients 3 and 4) received dexmedetomidine twice. In patient 3, hyperthermia occurred only during the second administration, with a 2-day interval in-between. In contrast, in patient 4, hyperthermia occurred only during the first administration, with a 6-day interval in-between.

As far as infectious diseases were concerned, 4 of 9 (44%) patients were under antibiotic therapy for endocarditis and/or pacemaker infection (patients 2, 4, and 6) and for pneumonia (patient 3). After the onset of hyperthermia, the antibiotic therapy was empirically changed or initiated in 4 of 9 (44%) patients (patients 1, 2, 4, and 7). Retrospectively, no unambiguous focus of infection was identified in any patient, and microbiological sampling results were negative for relevant pathogens. Table 1 presents the details of infection management and microbiological investigations for all patients.

Noninfectious causes present during hyperthermia are given in Table 2. One patient (patient 6) experienced a convulsive status epilepticus and 1 patient (patient 2) had a thrombosis in a jugular vein. In all patients, laboratory inflammation markers were elevated. As far as drug exposure was concerned, a temporal association with

hyperthermia was found exclusively for dexmedetomidine in all patients. The likelihood of an ADR was categorized by the WHO-UMC criteria as “probable” in all patients and by the Naranjo ADR scale as “probable” in 1 patient (patient 3) and “possible” in 8 patients (Table 1).

Individual case descriptions, a table summarizing all drugs given prior to or during dexmedetomidine exposure, and the Naranjo questionnaire scores are provided in Supplemental Digital Content 1–3, Material 1, <http://links.lww.com/AA/B942>, Table 1, <http://links.lww.com/AA/B943>, and Table 2, <http://links.lww.com/AA/B944>.

DISCUSSION

In this case series, we present 9 (4.5%) patients with clinically relevant hyperthermia of 200 patients with exposure to dexmedetomidine during a 2-year period in our ICU. The observed drug-effect relationship is highly suggestive of drug fever.³ Because our 9 patients represent a convenience sample, the true incidence of dexmedetomidine-associated hyperthermia in our ICU cannot be determined with certainty. However, in 2 multicenter, randomized trials involving ventilated ICU patients, pyrexia has been reported as an adverse drug event in the dexmedetomidine group in 16 of 247 (6.5%) patients (MIDEX trial) and in 13 of 246 (5.3%) patients (PRODEX trial).¹⁵ The Swiss Drug Compendium reports an incidence of between 1% and 10% of treated patients, without providing further details or references (<https://compendium.ch/mpro/mnr/23800/html/de>).

Our results are supported by several case reports that describe a similar pattern of hyperthermia during dexmedetomidine administration: onset of hyperthermia after dexmedetomidine initiation (range 3–24 hours), persistence of hyperthermia during dexmedetomidine administration (body temperature $>38^\circ\text{C}$ up to 7 days), and resolution of hyperthermia after dexmedetomidine discontinuation (range 2–12 hours).^{6–11} A summary of these case reports is presented in Table 3.

Drug fever is frequently considered a diagnosis of exclusion. Confounding factors are common particularly in critically ill patients, in which multiple pathologies and multiple drug treatments are usually present at the same time. Therefore, all infectious and noninfectious causes of hyperthermia must be excluded by a multimodal diagnostic workup.^{1,3}

In this case series, all patients admitted with an infection were under adequate antibiotic therapy. Retrospectively, no patient had a new focus of infection and/or a positive microbiological sampling result, rendering infections unlikely for the febrile episodes. However, the onset of hyperthermia triggered costly microbiological investigations in 8 of 9 (89%) patients and the initiation of an empirical antibiotic therapy in 4 (44%) of 9 patients, which might retrospectively be considered inappropriate.

In 3 published case reports, infections were confounding factors of fever during dexmedetomidine administration: Harding et al⁶ reported a patient with methicillin-resistant *Staphylococcus aureus* pneumonia and concurrent bacteremia, Faust and Sutton⁹ described a patient with hyperthermia during an acute exacerbation of chronic obstructive lung disease, and Lowenstein et al¹⁰ reported a patient after multiple organ transplantation with respiratory failure

Table 1. Patient Characteristics, Details of Dexmedetomidine Administration, Relationship of Infectious and Noninfectious Etiologies With Observed Hyperthermia, and Assessment of Results by Naranjo and WHO-UMC Criteria

Patient (#)	Admission Diagnosis and Details of Surgery	ICU Length of Stay (d)	DEX Start (POD)/ Total Duration (h); Duration of HT (h); Max. BT (°C); BT >38.5°C after DEX start (h); BT <38.5°C after DEX stop (h)	DEX Initial Dose/At Start of HT/At Max of HT (µg/kg/h)	Initiation or Change of Antibiotic Treatment Following DEX-Associated Hyperthermia	Infectious Etiology of Hyperthermia	Potential Noninfectious Etiology of Hyperthermia	Naranjo Score/Grading of ADR	WHO-UMC Causality Assessment
1	DCM Heart transplantation ECC 187 min, ACT 152 min	23	DEX: POD 1/9 h HT: 12 h Max. BT: 39.2°C BT >38.5°C: 4 h BT <38.5°C: 3 h	1.4/1.4/1.0	Initiation of tazobactam/piperacillin and vancomycin	Unlikely: no clinical or laboratory signs of infection	Inflammation after major surgery	4/possible	Probable
2	Endocarditis PM extraction MV repair PM implantation ECC 69 min, ACT 52 min	28	DEX: POD 7/26 h HT: 34 h Max. BT: 39°C BT >38.5°C: 6 h BT <38.5°C: 8 h	0.8/0.8/0.8	Change from tazobactam/piperacillin to meropenem; flucloxacillin and rifampicin preexisting	Unlikely: endocarditis under antibiotic treatment BC and UC: negative TC: <i>Stenotrophomonas maltophilia</i>	1. Thromboembolic disease (thrombus in internal jugular vein) 2. Inflammation after major surgery	4/possible	Probable
3	CHD OPCAB	9	DEX: POD 4/35 h HT: 36 h BT: 39°C BT >38.5°C: 5 h BT <38.5°C: 1 h	1.0/0.8/0.4	No change of antibiotics; amoxicillin/clavulanic acid preexisting	Unlikely: aspiration pneumonia under antibiotic treatment TC: negative	Inflammation after major surgery	6/probable	Probable
4	CRT pocket infection CRT system replacement	45	DEX: POD 1/116 h HT: 124 h Max. BT: 40°C BT >38.5°C: 10 h BT <38.5°C: 8 h	0.6/1.2/0.9	Initiation of tazobactam/piperacillin in addition to preexisting vancomycin and rifampicin	Unlikely: CRT-related infection under antibiotic treatment UC, BC, CVC: negative TC: flora of oral cavity	Inflammation after major surgery	3/possible	Probable
5	TAAA EVAR with renovisceral endodebranching	2	DEX: ICUD 1/4 h HT: 5 h Max. BT: 38.6°C BT >38.5°C: 2 h BT <38.5°C: 1 h	0.4/0.4/0.4	No antibiotics	Unlikely: COPD without clinical exacerbation TC: <i>Pseudomonas aeruginosa</i> BC: negative	Inflammation after major surgery	4/possible	Probable
6	Endocarditis and CHD AV replacement MV and TV repair CABG ECC 195 min, ACT 141 min	7	DEX: POD 1/5 h HT: 7 h Max. BT: 38.8°C BT >38.5°C: 2 h BT <38.5°C: 2 h	1.0/1.0/1.0	No change of antibiotics; vancomycin, rifampicin, and gentamycin preexisting	Unlikely: endocarditis under antibiotic treatment BC, UC, TC: negative	1. Temperature dysregulation (status epilepticus) 2. Inflammation after major surgery	4/possible	Probable

(Continued)

Table 1. Continued									
Patient (#)	Admission Diagnosis and Details of Surgery	ICU Length of Stay (d)	DEX Start (POD)/ Total Duration (h); Duration of HT (h); Max. BT (°C); BT >38.5°C after DEX start (h); BT <38.5°C after DEX stop (h)	DEX Initial Dose/At Start of HT/At Max of HT (µg/kg/h)	Initiation or Change of Antibiotic Treatment Following DEX-Associated Hyperthermia	Infectious Etiology of Hyperthermia	Potential Noninfectious Etiology of Hyperthermia	Naranjo Score/Grading of ADR	WHO-UMC Causality Assessment
7	VHD and CHD AV replacement CABG ECC 155 min, ACT 55 min	9	DEX: POD 2/34 h HT: 38 h Max. BT: 39°C BT >38.5°C: 21 h BT <38.5°C: 4 h	1.4/1.4/1.4	Initiation of tazobactam/piperacillin	Unlikely BC, CVC, TC: negative	Inflammation after major surgery	4/possible	Probable
8	VHD and CHD AV replacement CABG ECC 109 min, ACT 77 min	3	DEX: POD 1/25 h HT: 26 h Max. BT: 38.6°C BT >38.5°C: 7 h BT <38.5°C: 1 h	1.0/1.0/1.0	No antibiotics	Unlikely BC, UC, TC: negative	Inflammation after major surgery	4/possible	Probable
9	VHD MV repair ECC 169 min, ACT 123 min	29	DEX: POD 5/36 h HT: 53 h Max. BT: 39.2°C BT >38.5°C: 17 h BT <38.5°C: 17 h	0.5/1.3/1.3	No change of antibiotics; tazobactam/piperacillin and vancomycin preexisting	Unlikely BC, UC, TC, PAC: negative	Inflammation after major surgery	4/possible	Probable

Abbreviations: #, patient number; ACT, aortic clamp time; ADR, adverse drug reaction; AV, aortic valve; BC, blood culture; BT, body temperature; CABG, coronary artery bypass grafting; CHD, coronary heart disease; COPD, chronic obstructive lung disease; CRT, cardiac resynchronization therapy; CVC, central venous catheter; DCM, dilated cardiac myopathy; DEX, dexmedetomidine; ECC, extracorporeal circulation; EVAR, endovascular aortic repair; HT, hyperthermia; ICU, intensive care unit; ICUD, ICU day; MV, mitral valve; OPCAB, off-pump coronary artery bypass; PAC, pulmonary artery catheter; PM, pacemaker; POD, postoperative day; TAAA, thoracoabdominal aortic aneurysm; TC, tracheal aspirate culture; TV, tricuspid valve; UC, urine culture; VHD, valvular heart disease; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

Body temperature during dexmedetomidine administration

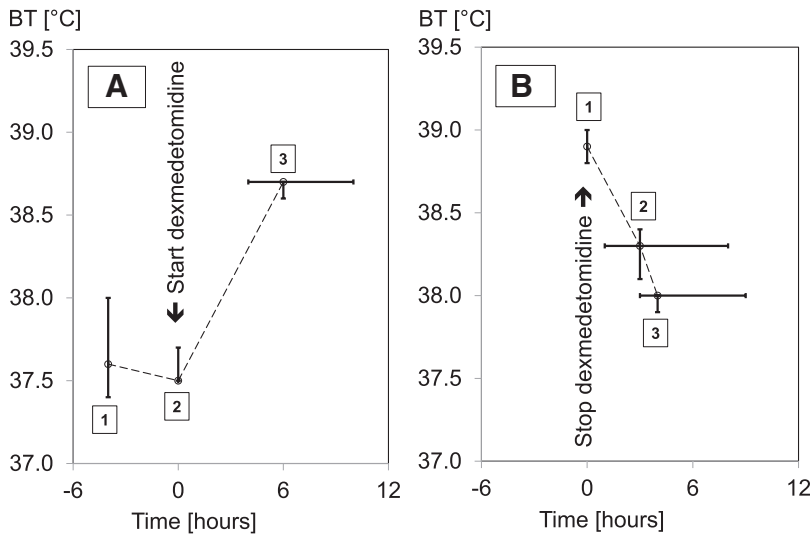


Figure. A and B, The body temperature (BT) of 9 patients over time in relation to dexmedetomidine (DEX) administration. Values are given as median (interquartile range). A, The time points indicate (1) 4 hours prior to DEX administration, (2) start of DEX administration, (3) first BT >38.5°C. B, The time points indicate (1) end of DEX administration, (2) resolution of hyperthermia ≤38.5°C, and (3) BT ≤38.0°C.

Table 2. Noninfectious Etiologies of Hyperthermia, Differential Diagnoses of All Case Series Patients and Likelihood of a Relationship With Observed Hyperthermia

Noninfectious Etiology of Hyperthermia	Differential Diagnosis of Case Series Patients With Potential for Hyperthermia	Relationship of Differential Diagnosis With Observed Hyperthermia Period
Central temperature dysregulation	# 2 and 6: status epilepticus # 3: out of hospital cardiac arrest	Possible for # 6
Drugs	All patients	Possible: presence of a temporal relationship only for DEX
Endocrine disorders	No patient	...
Heat stroke	No patient	...
Immunological and inflammatory diseases	# 2: history of ANA-positive rheumatoid disease	Unlikely: clinically no active lesion, hydrocortisone administration postoperative
Malignancy	# 9: history of metastasized neuroendocrine tumor in pancreas	Unlikely
Metabolic disorders	# 1 and 4: history of gout	Unlikely: absence of a clinically active lesion
Reactions to blood products	All patients, except for # 8	Unlikely: absence of a temporal relationship
Inflammation after tissue destruction	All patients: after major surgery	Possible: inflammatory blood markers above normal range
Thromboembolic disease	# 2: thrombus in a jugular vein	Possible

Adapted from Rehman and deBoisblanc⁴ and Walter et al.⁴
Abbreviations: #, patient number; ANA, antinuclear autoantibodies; DEX, dexmedetomidine.

following aspiration. In all these patients, great efforts and resources were spent to exclude infections, reflecting the difficulties in daily praxis to correctly diagnose drug fever in time.

The screening of our patients for noninfectious causes of fever revealed 3 common factors. First, 8 of 9 patients had received blood products, but transfusion reactions were considered unlikely in the absence of a temporal relationship with hyperthermia. Second, all patients had laboratory signs of an inflammatory response to major surgery. Third, all patients had received several drugs in common (Supplemental Digital Content 2, Table 1, <http://links.lww.com/AA/B943>), but a temporal relationship with hyperthermia was only found for dexmedetomidine.

This drug-effect relationship was assessed by 2 ADR causality assessment methods.¹³ The WHO-UMC algorithm favored a higher ratio of “probable” ADR cases (100%) than

the Naranjo ADR scale (11%). Differences in the level of causality between ADR algorithms have been described,^{13,14} and the incongruence of our results is explained by methodological differences. Infectious and noninfectious causes for hyperthermia were considered possible, but unlikely, in our patients. According to the WHO-UMC criteria, this was best reflected by the category “probable.” As for the Naranjo ADR scale, the deduction of 1 point for possible alternatives of hyperthermia placed all patients but one in the category “possible.” It was the drug-effect reaction pattern that placed patient 3 in the category “probable.”

The Naranjo assessment was used in 2 of the published case reports: the association between dexmedetomidine and hyperthermia was categorized “possible” in a patient following cardiac surgery⁸ and “probable” in a patient with exacerbated chronic obstructive lung disease.⁹ A “definite” or “certain” drug-effect relationship, the highest ADR

Table 3. Published Case Reports Describing Hyperthermia During Dexmedetomidine Administration

Case Report and Year of Publication	Admission/Primary Diagnosis and Details of Treatment	Indication for DEX in the ICU and Start of Treatment	Duration of DEX Treatment, Duration of HT, Rise and Fall of BT After Start and Stop of DEX	DEX Initial Dose/At Start of HT/At Max of HT (µg/kg/h)	Max. BT (°C)	Suspected Etiology/Differential Diagnosis of Hyperthermia, Treatment, and/or Diagnostic Steps	Proposed Mechanism of Drug Fever and Relevant Comments From the Authors	DEX Rechallenge/Occurrence of HT	Naranjo Score/Grading of ADR
Okabe et al (2009) ¹¹	AAA rupture Replacement of abdominal aorta by emergent open surgery	Sedation during mechanical ventilation POD 6 and 10	DEX: POD 6 and 7 HT: POD 7 Re-DEX: POD 10–15 HT: POD 11–15 BT 39.2°C after DEX start: 22 h BT 36.5°C after DEX stop: 7 h	DEX: 0.7/0.5/0.5 Re-DEX: 0.4/0.4/0.7	40.6	1. Exclusion of infection/sepsis: MB sampling: BC, UC, sputum culture negative; change of CVC and of antibiotics; CT of chest and abdomen 2. Administration of anti-inflammatory drugs 3. Administration of dantrolene 4. Collagen disease 5. Allergic reaction	Allergic reaction to DEX with sensitization during initial administration	Yes/Yes	...
Harding et al (2013) ⁶	Pneumonia with MRSA bacteremia Antibiotic treatment (cefepime and vancomycin)	Sedation during mechanical ventilation ICUD 2	DEX: 12 hours HT: 15 h BT 37.5°C after DEX start: 3 h BT "normal" after DEX stop: 12 h	1.0/1.5/...	40.6	Critical review of therapeutic management	Activation of α ₂ c adrenergic receptor by high-dose DEX (described for MDMA but not for DEX)	No	...
Miyazaki et al (2013) ⁷	#1: VHD, CHD Replacement of AV and ascending aorta CABG #2: DCM with heart failure 1. Medical treatment 2. Ablation of atrioventricular node	#1 and #2: Sedation during mechanical ventilation #1: ICUD 1 #2: ICUD 1 #2: Re-DEX ICUD 4	#1: DEX 11 d HT >37.5°C: approx. 10 d BT >38.0°C after DEX start: "hours" Normalization of BT after DEX stop: "hours" #2: DEX 7 d HT >37.5°C: 6 d BT >38.0°C after DEX start: approx. 24 h BT normalization after DEX stop: 'hours' #2: Re-DEX: 3.5 d HT >37.5°C: 2.5 d BT >38.0°C after DEX start: approx. 24 h BT 37°C after DEX stop: 'hours'	#1: 0.4/0.4/0.4 #2: 0.4/0.7/0.4 #2 Re-DEX: 0.4/0.4/0.4	#1: 39.6 #2: 39.6	#1: Infection: VAR, MB sampling (UC, BC, sputum); change of antibiotics: ampicillin/sulbactam, meropenem, vancomycin #2: Infection: initiation of meropenem, MB sampling: BC, UC, CVC, sputum negative	Potential influences on BT regulation mediated by α ₂ receptors	#1: No #2: Yes/Yes	...

(Continued)

Table 3. Continued

Case Report and Year of Publication	Admission/Primary Diagnosis and Details of Treatment	Indication for DEX in the ICU and Start of Treatment	Duration of DEX Treatment, Duration of HT, Rise and Fall of BT After Start and Stop of DEX	DEX Initial Dose/At Start of HT/At Max of HT (µg/kg/h)	Max. BT (°C)	Suspected Etiology/Differential Diagnosis of Hyperthermia, Treatment, and/or Diagnostic Steps	Proposed Mechanism of Drug Fever and Relevant Comments From the Authors	DEX Re-challenge/Occurrence of HT	Naranjo Score/Grading of ADR
Reeve and Cooper (2013) ⁸	Myocardial infarction, MV replacement, CABG POD 2: SIRS/septic shock, antibiotic treatment (ceftriaxone, piperacillin/tazobactam, levofloxacin, vancomycin)	Sedation during mechanical ventilation POD: 5	DEX: 20.5 h HT: 16.5 h BT 39.4°C after DEX start: 8 h BT 38.4°C after DEX stop: 2 h	0.8/0.8/0.8	40.6	1. Physical cooling with ice 2. Exclusion of hyperthyroidism (blood tests) and seizure (EEG), consideration of malignant hyperthermia 3. Infection: all antibiotics stopped before DEX initiation 4. Lidocaine drug fever	None	No	3/possible
Lowenstein et al (2015) ¹⁰	Respiratory failure following aspiration Antibiotic treatment ("broad spectrum," levofloxacin) History of heart, liver, kidney transplantation	Sedation during mechanical ventilation	Onset of HT after DEX initiation Fever absent after DEX stop: 12 h	...	40	1. Exclusion of infection: MB-sampling: UC, repeated BC (negative), chest x-ray, surgery of stage IV decubitus ulcer (no infection) 2. Exclusion of vein thrombosis by US	None	No	-
Faust and Sutton (2015) ⁹	Acute exacerbation of COPD Antibiotic (levofloxacin) and IV-steroid (methylprednisolone) treatment	Sedation during mechanical ventilation	DEX: 77 h HT: 66 h BT 38.1°C after DEX start: 24 h "Afebrile" after DEX stop: 3 h	0.2/0.3–0.5/ 0.3–0.5	40.3	1. Exclusion of infection: "cultures" (sterile), vancomycin single shot 2. Exclusion of hyperthyroidism (laboratory results) 3. Exclusion of seizure ("exam") 4. Exclusion of NMS (no signs, patient history)	Drug fever with a potential dose-effect relationship	No	5/probable

Abbreviations: #, patient number; AAA, abdominal aortic aneurysm; ADR, adverse drug reaction; AV, aortic valve; CABG, coronary artery bypass grafting; BC, blood culture; BT, body temperature; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CVC, central venous catheter; DCM, dilated cardiac myopathy; DEX, dexmedetomidine; EEG, electroencephalography; HT, hyperthermia; ICU, intensive care unit; ICUD, ICU day; MB, microbiological; MDMA, 3,4-methylenedioxymethamphetamine; MRSA, methicillin-resistant *Staphylococcus aureus*; MV, mitral valve; NMS, neuroleptic malignant syndrome; POD, postoperative day; Re-DEX, dexmedetomidine readministration; SIRS, systemic inflammatory response syndrome; UC, urine culture; US, ultrasound; VAP, ventilator associated pneumonia; VHD, valvular heart disease; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

grading category, between dexmedetomidine and hyperthermia has not been described yet.

Febrile disorders during dexmedetomidine administration have been reported as ADRs to the WHO global pharmacovigilance database (<http://www.vigiaccess.org>). However, adverse events reported to these databases usually lack detailed case information, and the assessment of the causal relationship to the drug is often not possible. Drugs may cause fever by several mechanisms: (1) drug effects on thermoregulation, (2) drug administration-related reactions, (3) pharmacologic drug actions, (4) idiosyncratic responses, and (5) hypersensitivity/immunologic reactions, which are the most common.³ However, the results of this case series and the published case reports are not entirely explained by one common mechanism. The drug-effect reaction pattern of patient 3 with the occurrence of hyperthermia exclusively during the rechallenge of dexmedetomidine might point to an immunologic/allergic mechanism, which was also considered possible in the case report of Okabe et al.¹¹ However, dexmedetomidine did not trigger a uniform reaction during the rechallenge in patient 4 of this case series. Furthermore, to the best of our knowledge, hyperthermia occurred during the first exposure to dexmedetomidine in the other case series patients, which in summary questions an underlying immunologic mechanism. Alternatively, an influence on thermoregulation by α_2 -agonists has been proposed in 1 published case report.⁷ However, in this case series, no dose-dependent effect of dexmedetomidine on the occurrence of hyperthermia was found, as assumed by Harding et al⁶ and Faust and Sutton.⁹ Of interest, a preclinical study in rodents investigated antipyretic properties of α_2 -agonists, including dexmedetomidine, and demonstrated an inhibition of brown adipose tissue and shivering thermogenesis.¹⁶ This cannot per se be used as an argument against dexmedetomidine-induced hyperthermia, but instead underlines the need for further research to investigate the corresponding mechanism.

In summary, we described 9 critically ill patients with the onset of clinically relevant hyperthermia during dexmedetomidine administration, highly suggestive of drug fever. As risk factors and underlying mechanisms are uncertain to date, further research on this topic is warranted. ■■

DISCLOSURES

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Contribution: This author helped interpret the data and critically revised the manuscript.

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REFERENCES

1. Rehman T, deBoisblanc BP. Persistent fever in the ICU. *Chest*. 2014;145:158–165.
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:801–810.
3. Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30:57–69.
4. Walter EJ, Hanna-Jumma S, Carraretto M, Forni L. The pathophysiological basis and consequences of fever. *Crit Care*. 2016;20:200.
5. Keating GM. Dexmedetomidine: a review of its use for sedation in the intensive care setting. *Drugs*. 2015;75:1119–1130.
6. Harding A, Heine A, Gerlach A. Dexmedetomidine induced hyperthermia. *Crit Care Med*. 2013;41:A340.
7. Miyazaki Y, Sato K, Shirai N, Shirai H, Sai S, Adachi T. Two cases of hyperthermia during administration of dexmedetomidine. *J Jpn Soc Intensive Care Med*. 2013;20:257–260.
8. Reeve AR, Cooper BE. Dexmedetomidine-induced fever. *J Pharm Technol*. 2013;29:215–218.

9. Faust AC, Sutton SE. Dexmedetomidine-associated fever in the intensive care unit. *Ther Adv Drug Saf.* 2015;6:234–237.
10. Lowenstein M, Yoo A, Glass M. Dexmedetomidine: a perplexing pyrogen. *J Gen Intern Med.* 2015;30:S385.
11. Okabe T, Takeda S, Akada S, Hongo T, Sakamoto A. Postoperative intensive care unit drug fever caused by dexmedetomidine. *Anesth Analg.* 2009;108:1589–1591.
12. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239–245.
13. Kane-Gill SL, Forsberg EA, Verrico MM, Handler SM. Comparison of three pharmacovigilance algorithms in the ICU setting: a retrospective and prospective evaluation of ADRs. *Drug Saf.* 2012;35:645–653.
14. Varallo FR, Planeta CS, Herdeiro MT, Mastroianni PC. Imputation of adverse drug reactions: causality assessment in hospitals. *PLoS One.* 2017;12:e0171470.
15. Jakob SM, Ruokonen E, Grounds RM, et al; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA.* 2012;307:1151–1160.
16. Madden CJ, Tupone D, Cano G, Morrison SF. α_2 Adrenergic receptor-mediated inhibition of thermogenesis. *J Neurosci.* 2013;33:2017–2028.