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MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Differentiating probable nitrofurantoin-induced drug fever from antipsychotic-induced hyperthermia in a patient receiving clozapine

Stephen B. Vickery, PharmD, BCPS[1]
Andrew D. Burch, PharmD Candidate[2]
P. Brittany Vickery, PharmD, BCPS, BCPP, CPP[3]

How to cite: Vickery SB, Burch AD, Vickery PB. Differentiating probable nitrofurantoin-induced drug fever from antipsychotic-induced hyperthermia in a patient receiving clozapine. Ment Health Clin [Internet]. 2022;12(3):205-9. DOI: 10.9740/mhc.2022.06.205.

Submitted for Publication: May 10, 2021; **Accepted for Publication:** February 7, 2022

Abstract

Nitrofurantoin (NIT) is a commonly utilized antibiotic for the treatment of UTIs. Although well tolerated, NIT is not without potential adverse reactions. This case report details the observation of probable NIT-induced drug fever in a patient receiving clozapine. A 61-year-old female with treatment-refractory schizoaffective disorder was admitted to a psychiatric unit with paranoia and auditory hallucinations, prompting clozapine initiation during day 1 of hospitalization. Due to worsening hallucinations and anxiety, antibiotic therapy with NIT for a presumed UTI was initiated 8 days after admission. Febrile episodes were observed beginning on hospital day (HD) 9, leading to concern for possible neuroleptic malignant syndrome (NMS), which led to clozapine discontinuation. The patient received a total of 3 doses of NIT with continued fever until discontinuation on HD 10. No further complications were encountered, and clozapine was safely resumed on HD 13. Although sparsely described in the medical literature, occurrences of drug fever attributable to NIT are previously reported. A review of the medical literature identified only 5 previously published articles specific to NIT-induced drug fever, none of which specified interruptions of psychotropic therapy for a patient with acute psychiatric decompensation. This case highlights the differential diagnosis of fever related to NIT in a patient receiving clozapine when NMS was initially suspected.

Keywords: nitrofurantoin, drug fever, neuroleptic malignant syndrome, clozapine

[1] (Corresponding author) Assistant Professor, Wingate University School of Pharmacy, Hendersonville, North Carolina, s.b.vickery@wingate.edu, ORCID: https://orcid.org/0000-0003-1623-9983; [2] PharmD Student, Wingate University School of Pharmacy, Hendersonville, North Carolina, ORCID: https://orcid.org/0000-0003-2547-0984; [3] Associate Professor, Wingate University School of Pharmacy, Hendersonville, North Carolina, ORCID: https://orcid.org/0000-0002-1059-8371

Disclosures: The authors report no financial conflicts. Additionally, no financial support was received for the research, authorship, and/or publication of this article.

Background

With more than 50 years of clinical use, nitrofurantoin (NIT) is a safe anti-infective agent with a reported side effect occurrence of 1 out of every 100 000 patients treated over the total treatment course.[1] Nevertheless, NIT use is associated with adverse events, including gastrointestinal, pulmonary, and hepatic toxicity.[2] Of importance, the risk of adverse events, most notably with pulmonary toxicity, is greater in individuals of increased age and with chronic use.[3,4] Short durations of therapy (less than 2 weeks) are associated with mild toxicity with low risk of hypersensitivity reactions.[5]

Drug fever (DF) is a rare drug reaction, resulting in hyperthermia with prompt resolution following therapy discontinuation. The incidence of DF is approximately 4% across all observed adverse drug reactions (ADRs) and can be encountered in up to 1 in 10 inpatients.[6] Medications frequently associated with DF include antimicrobials,

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antiepileptics, and antiarrhythmics.[7] DF is generally considered a diagnosis of exclusion after other causes of hyperthermia have been ruled out and the suspected offending medication has been removed.[8] NIT-induced DF is not a new phenomenon but is scarcely reported in the medical literature. This case report highlights the differential diagnoses considered for a patient with hyperthermic episodes, namely, neuroleptic malignant syndrome (NMS), prompting antipsychotic interruption, and the evaluation of NIT as the offending agent.

Case Report

A 61-year-old female with a history of treatment-refractory schizoaffective disorder, bipolar type, and generalized anxiety disorder presented to our hospital's emergency department with complaints of paranoia and auditory hallucinations. According to the referral, she was experiencing delusions; frequently calling the sheriff's department; walking in the road; and experiencing anxiety, poor judgment, and poor sleep. The patient denied suicidality; however, she had made comments related to shooting herself. Her past psychiatric history was notable for previous hospitalization approximately 1 year prior with similar symptoms. Past medical history was significant for hypertension, hyperlipidemia, hypothyroidism, and gastritis. Her psychiatric family history was significant for maternal depression. Home medications included amlodipine 5 mg by mouth daily, aripiprazole 10 mg by mouth daily, aspirin 81 mg by mouth daily, fluticasone 1 spray each nostril daily, levothyroxine 88 mcg by mouth daily in the morning, loratadine 10 mg by mouth daily, lithium 600 mg by mouth with breakfast and 900 mg by mouth with supper, lorazepam 0.5 mg by mouth 3 times daily as needed for anxiety, melatonin 3 mg by mouth at bedtime as needed for sleep, simvastatin 40 mg by mouth at bedtime, omega-3 1000 mg by mouth daily, ziprasidone 80 mg by mouth at bedtime, and trazodone 200 mg by mouth at bedtime as needed for sleep. Upon emergency department assessment, the patient endorsed dysuria and urinary frequency, prompting urinalysis with culture reflex obtainment. Admission vitals (hospital day [HD] 1) included temperature 36.6°C, BP 156/76 mm Hg, heart rate (HR) 62 to 73 beats/min (bpm), respiration rate (RR) 16 breaths/min. Laboratory data revealed serum creatinine 0.6 mg/dL, estimated creatinine clearance 92.7 mL/min, WBC 10.4 K/µL, absolute neutrophil count (ANC) 7.2 K/µL, and eosinophils 1.4%. Clean-catch midstream urinalysis testing yielded a small amount of blood, negative nitrites, trace leukocyte esterase, 0 to 2 WBCs, 3 to 5 red blood cells, and rare bacteria. Due to the presence of leukocyte esterase, a reflex urine culture was performed. However, upon transfer to the psychiatric unit (HD 1), the patient denied her previously endorsed UTI symptoms. As a result, antibiotic therapy was not initiated.

Previous antipsychotic administration included ziprasidone 80 mg by mouth at bedtime in combination with aripiprazole 10 mg by mouth daily, which the patient expressed did not help her delusions or hallucinations. Risperidone and paliperidone were also both ineffective. Quetiapine made her feel disoriented and gain weight; olanzapine and lurasidone provided no relief of her symptoms. Doses and durations of previous antipsychotic medications were unknown by the patient, and records could not be located.

Given her poor response to previous antipsychotic medications, clozapine 12.5 mg daily was initiated in conjunction with aripiprazole and ziprasidone discontinuation. All other home medications were continued at current doses, and acetaminophen 650 mg orally every 4 hours as needed for pain and magnesium hydroxide 30 mL suspension orally for constipation were used on day 2. Intramuscular ziprasidone and oral olanzapine were available as needed for psychosis but not utilized. Psychiatric symptoms present upon admission were still noted on HD 3; titration of clozapine to 75 mg twice daily occurred by HD 7 with improvement in symptoms. A trough lithium concentration was evaluated and was 1.05 mmol/L. On HD 8, the patient began displaying worsening hallucinations, paranoia, anxiety, and confusion. Additionally, there were no extrapyramidal symptoms or muscular rigidity. Vitals were notable for temperature 37.1°C, BP 115/65 mm Hg, HR 89 to 90 bpm, RR 20 breaths/min. Blood cultures from admission finalized without growth. Urine culture from admission yielded >100 000 CFU/mL *Escherichia coli* with resistance to ampicillin, ampicillin-sulbactam, and trimethoprim-sulfamethoxazole. Due to the patient's new onset decompensation with positive urine culture results, NIT 100 mg twice daily was initiated (HD 8). On HD 9, the patient was found to be lethargic and became febrile (39.3°C) within hours following the second NIT dose (time course summarized graphically in the Figure). Review of systems was unremarkable except for back pain, somnolence, and lethargy. Physician examination noted no signs of extrapyramidal symptoms or tardive dyskinesia. Objective information included BP 115/71 mm Hg, HR 87 to 89 bpm, RR 18 breaths/min, WBCs 7.0 K/µL, serum creatinine 0.6 mg/dL, and estimated creatinine clearance 92.7 mL/min. Due to concern for toxicity, a clozapine concentration was obtained, and the evening dose was held. The patient remained febrile overnight and defervesced early into HD 10. During the time of defervescence, the patient received her third NIT dose and was taking acetaminophen as needed for fever. Approximately 6 hours following the third NIT administration, the patient again became febrile (38.9°C). Vitals during this time demonstrated BP 121/68 mm Hg, HR 79 to 98 bpm, RR 18 breaths/min. Other

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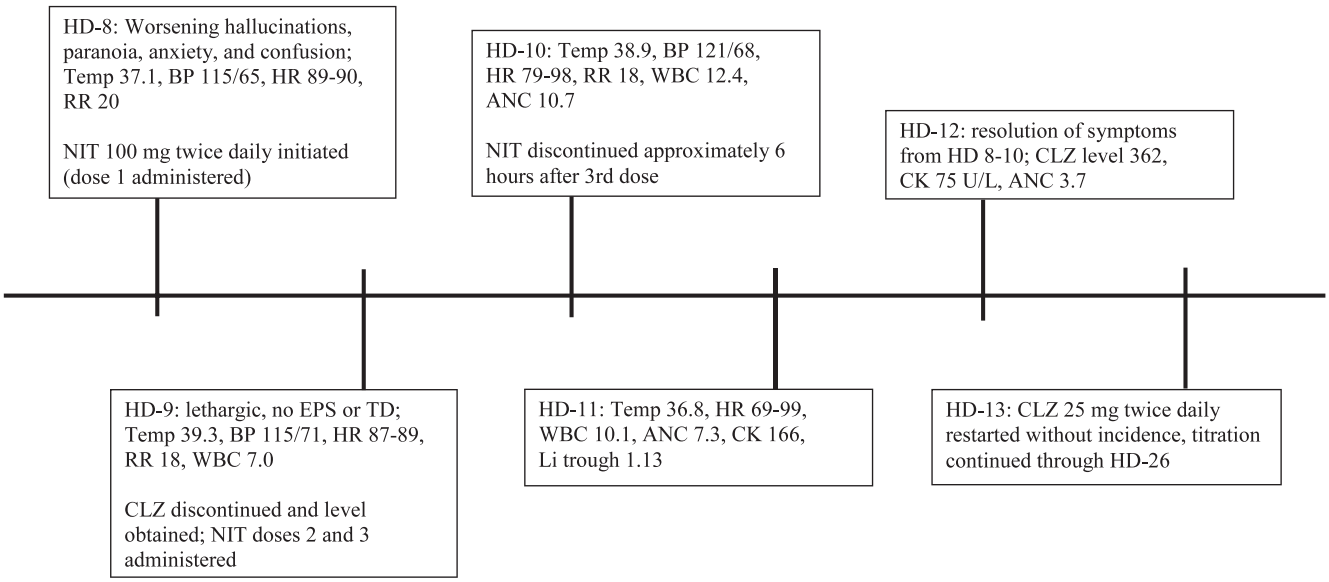

FIGURE: Time course of medication administration and laboratory assessment (ANC = absolute neutrophil count [K/μL]; BP = in mm Hg; CK = creatinine kinase [U/L]; CLZ = clozapine [ng/mL]; EPS = extrapyramidal symptoms; HD = hospital day; HR = heart rate [beats/min]; Li = lithium [mmol/L]; NIT = nitrofurantoin; RR = respiratory rate [breaths/min]; TD = tardive dyskinesia; temp = in °C; WBC = in K/μL)

objective information yielded WBC 12.4 K/μL, ANC 10.7 K/μL, eosinophils 0.1%, and creatine kinase (CK) 163 U/L (morning) and 250 U/L (evening). An electrocardiogram demonstrated normal sinus rhythm, and a posteroanterior and lateral chest x-ray noted known left rib fractures with no new abnormality. This new febrile state persisted for approximately 15 hours and then resolved. NIT was discontinued following this second febrile period; in total, the patient received 3 doses. On HD 11, the patient was without fever, HR 69 to 99 bpm, and observed improvement in blood counts (WBC 10.1 K/μL, ANC 7.3 K/μL) and CK (166 U/L). Additionally, a lithium trough concentration resulted at 1.13 mmol/L. On HD 12, the patient reported resolution of all previous symptoms. The clozapine concentration from HD 9 resulted at 362 ng/mL (reference range: 350 to 600 ng/mL); other labs included CK 75 U/L and ANC 3.7 K/μL. The following day, HD 13, clozapine 25 mg twice daily was restarted without incident. Clozapine titration continued through HD 26 with noted patient stabilization and psychiatric symptom resolution. The patient was discharged on HD 27 with an ANC of 4.2 K/μL on a monotherapy regimen of clozapine 150 mg every morning and 100 mg every evening. All other home medications continued throughout the hospitalization were resumed for continued use, and the patient was given appropriate follow-up and outpatient support.

Discussion

Observed hyperthermic episodes require evaluation of both medication history and clinical features. Of interest for our patient, the differential diagnosis contained several etiologies that were investigated. Given the observation of antipsychotic administration, NMS was of first consideration, prompting clozapine discontinuation. This was eventually ruled out due to the lack of altered mental status, muscle rigidity, and autonomic instability commonly attributed to NMS.[9] Furthermore, objective and laboratory assessments were inconsistent with traditional diagnostic criteria.[10,11] The prospect of clozapine-induced fever (CIF) was then considered. CIF is a benign hyperthermia that can develop in upward of half of treated patients, most commonly during the first month of treatment.[12] Temperatures are typically <40°C and are not related to dose-dependent exposure.[13] CIF does not require treatment cessation; as clozapine was discontinued due to concern for NMS, we recognize this as a limitation to establishing the role of clozapine in the patient's febrile episodes. Last, given the time course of medication administration and symptomatic observation, DF secondary to NIT administration was ultimately identified as the most likely explanation. Utilization of the Naranjo ADR Probability Score demonstrated a probable (score of 6) relationship between NIT and DF.[14]

Febrile episodes of DF demonstrate a temporal association of medication administration and fever occurrence.[15] Fever onset and degree of hyperthermia can vary with occurrence but usually range from 7 to 10 days and 38°C to 40°C, respectively.[15,16] Fever patterns can also vary; however, they are likely to occur in irregular intervals with periods of resolution or fluctuation.[15] Of interest, our patient's fever onset occurred earlier in treatment than

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the documented range in the medical literature. Patients with DF usually present "relatively well for their degree of fever."[7(p877)] Whereas fever may be the only objective sign, laboratory analysis can reveal elevations in eosinophils, erythrocyte sedimentation rate, hepatic transaminases, and lactic dehydrogenase.[7,15] An important clinical feature useful in the detection of DF is relative bradycardia (RB), a heart rate that does not increase proportionally with observed temperature elevation. Our patient displayed RB during HDs 9 and 10 following NIT administration. With observed temperatures of 39.3°C and 38.9°C, the expected pulse response should have been approximately 110 bpm.[17] Of note, the observation of RB is of diagnostic uncertainty in patients receiving medications that inhibit sinoatrial or atrioventricular node activity (eg, beta-blockers, nondihydropyridine calcium channel blockers) or those with arrhythmias or pacemaker-controlled rhythm.[7,15] As neither of these criteria applied to our patient, we attributed her observed RB to DF in the absence of other applicable diagnoses.

Available literature[18-22] highlights that NIT-induced DF is an infrequently encountered ADR with likely development in the first week of therapy, laboratory abnormalities and cutaneous manifestations, and resolution following discontinuation. A cohort of hospitalized patients from 1967 to 1968 receiving NIT and sulfonamides were prospectively reviewed for the observation of adverse reaction occurrence.[18] DF occurred more in the NIT group (2.0%) than the sulfonamide group (1.2%). NIT-induced allergic reactions were associated with greater morbidity than sulfonamide-induced allergic reactions. This observation was based on greater extracutaneous reactions with NIT than in the sulfonamide group. Last, reactions were most likely to occur within the first 7 days with an increased probability of reactions with each subsequent day of therapy. The Swedish ADR published an analysis of adverse reactions attributed to NIT over a 10-year period from 1966 to 1976.[19] Allergic reactions (consisting of fever as a symptom) were responsible for 42% of all documented events. Furthermore, fever occurrence (≥38°C) was the most common symptom prompting medical evaluation. As with the previous study, allergic complications were more likely observed with short-term treatment when compared with prolonged treatment. Between 1975 and 1980, 12 hospitalized patients were identified through infectious disease consultation wherein the observation of unexplained fever was thought attributable to ADR.[20] NIT was associated with 1 case, a 46-year-old woman treated for UTI. Fever occurred 6 days into treatment with a peak temperature of 38.9°C and subsided 2 days following discontinuation. Additionally, the patient displayed peripheral eosinophilia with noted rash and pulmonary infiltrates. Harris and Holdsambeck[21] reviewed the charts of every patient evaluated with a diagnosis of DF over the course of a 2-year period, 1984 to 1985. NIT was implicated in 1 case of DF; a 69-year-old woman receiving treatment for UTI. No information was provided regarding the duration of time from therapy onset to fever or time of defervescence following discontinuation; peak temperature was reported as 38.3°C. Of note, eosinophilia was not observed, and the patient displayed interstitial pneumonitis, suggesting chronic exposure to NIT. Last, a case report[22] highlighted the temporal nature of drug exposure and development of DF. The patient, a 77-year-old male, was given NIT for UTI prophylaxis on 4 separate occasions, each resulting in fever (≥38.1°C) shortly after administration. Complicating the recognition of NIT-induced DF was the observation of leukocytosis and bandemia, resulting in subsequent broad-spectrum antimicrobial administration. No mention of eosinophilia or pulmonary toxicity was described for any of the 4 presentations. Following eventual NIT discontinuation, the patient's fever and leukocytosis both resolved.

The variability of presentation among the reported cases highlights the complexity of recognition of drug-induced ADRs. Similarly to reported findings, our patient developed fever early into treatment within hours of drug administration. Discrepancies exist regarding the occurrence of eosinophilia and cutaneous manifestations. Our patient had an elevated eosinophil count but not one that would rise to the designation of eosinophilia as classified in the preceding studies (≥5% of total peripheral count). Furthermore, this patient was without any concern of rash or pulmonary toxicity. The lack of features associated with psychiatric ADRs such as NMS, occurrence of fever following drug administration, observation of relative bradycardia, and resolution of symptoms following discontinuation support the diagnosis of NIT-induced DF.

Conclusion

This case report underscores the ambiguity surrounding recognition of drug-induced adverse events. Additionally, it demonstrates the probable development of NIT-induced DF amid diagnostic consideration of NMS secondary to clozapine administration along with potential for clozapine-induced fever. Of importance for this patient was the impact of this ADR, interruption of clozapine titration during an acute psychiatric episode, and the resulting prolonged hospital stay for stabilization. Prompt medical review is necessary in the evaluation of the febrile patient. Providers are often aware of common etiologies of fever development, but unlikely culprits should be considered in cases of diagnostic uncertainty. As NIT is implicated in cases of DF, its role should be considered in the differential of the febrile patient receiving therapy. Timely recognition and medication cessation are paramount toward fever resolution.

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