Topics in Primary Care Medicine

Drug Fever

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Untoward drug reactions occur in about 15% of hospital inpatients and 5% of medical hospital admissions result from drug reactions. Fever may accompany the systemic and cutaneous manifestations of a drug reaction, but it rarely occurs as the sole feature, accounting for only 3% to 4% of all drug reactions. It is important to differentiate drug fever from fever of other causes to avoid costly and potentially harmful investigation and administration of inappropriate therapy.

Thermoregulation

Body temperature is maintained at 37°C (98.6°F) by the thermoregulatory center, located in the anterior hypothalamus, which controls the balance of heat production and peripheral heat loss. During fever, the thermostat setting in the hypothalamic center shifts upward, signaling for increased heat production and decreased peripheral heat loss. Several substances in addition to infectious agents have been recognized to cause fever. These are called exogenous pyrogens and are derived from various microbial and nonmicrobial sources. Exogenous pyrogens have no direct effect on the hypothalamus but rather produce fever through the mediation of a molecule previously described as endogenous pyrogen but now included in the term interleukin 1. The term interleukin 1 includes endogenous pyrogen, lymphocyte-activating factor, B-cell-activating factor and helper peak 1. At present, interleukin 1 is thought to be either a polypeptide derived from a single gene or a group of related peptides produced by a family of closely related genes.

Interleukin 1 is produced primarily from phagocytic cells. The primary sources are blood monocytes, phagocytic lining cells of the liver and spleen and other tissue macrophages; specialized cells such as keratinocytes, gingival and corneal epithelial cells, renal mesangial cells and brain astrocytes also produce interleukin 1-like molecules. Interleukin 1 enters the circulation and affects distant organ systems, acting as a hormone mediating a host's responses to infection and inflammation.

Fever is a prominent sign of the acute-phase response and is the result of the action of interleukin 1 on the thermoregulatory center in the brain. Interleukin 1 initiates fever by inducing an abrupt increase in the synthesis of prostaglandins, most notably prostaglandin E_2, in the anterior hypothalamus. The elevated prostaglandin levels in the hypothalamus raise the thermostatic set point and drive the mechanisms of heat conservation (vasoconstriction) and heat production (muscle shivering) until the blood and core temperature are elevated to match the hypothalamic set point. Inhibition of brain prostaglandin synthesis by antipyretics results in a lowering of body temperature.

Pathophysiologic Classification

As shown in Table 1, the causes of drug fever can be divided into five groups.

1. Hypersensitivity Reaction

Hypersensitivity reaction is the most common cause of drug fever. Rash, urticaria, eosinophilia, serum sickness or drug-induced systemic lupus erythematosus may accompany the fever. Fever unassociated with other symptoms occurs in 3% to 4% of patients with drug hypersensitivity reactions. Drugs such as sulfonamides, penicillin, phenytoin, barbiturates and methyldopa may cause serum sickness. Fever in these patients is associated with rash, lymphadenopathy, arthritis, nephritis and edema and can be easily recognized as an allergic reaction to a drug. After the initial hypersensitivity reaction, readministration of the drug, even after years,

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causes an accelerated reaction. Fever from drug hypersensitivity occurs more often in patients with atopy, severe infections and systemic lupus erythematosus.

The following are some of the frequently administered drugs that cause fever due to hypersensitivity (Table 2).

Antibiotics. Penicillin and sulfas are the most common antibiotics reported to cause fever. Other antibiotics, including streptomycin, vancomycin, tetracycline, sulfonamides, nitrofurantoin, demeclocycline hydrochloride and methicillin sodium, have also been implicated. The fever usually appears within the first week of administration, often resulting in the addition of another antibiotic.

Phenytoin. The clinical manifestations of phenytoin (diphenylhydantoin) hypersensitivity reaction vary from fever only to a fulminant illness consisting of vasculitis and disseminated intravascular coagulation. High fever may be accompanied by generalized lymphadenopathy and hepatosplenomegaly, a syndrome called pseudolymphoma. Symptoms occur anywhere from two to six weeks after the drug is administered and disappear after the drug is withdrawn. Recurrence has been elicited by readministration of the drug. Circulating antibodies against phenytoin have been shown in some cases. The presence of leukocytoclastic vasculitis in one reported case strongly suggests an immunologic basis for the reaction.

Methyldopa. Fever has been reported in 1% to 6% of patients taking methyldopa, occurring one to three weeks after starting the initial therapy. Temperature ranges from 37.7°C to 41.5°C (100°F to 106.7°F). Most patients have associated symptoms of malaise, chills and diarrhea and a third have abnormal results on liver function tests. A syndrome resembling septic shock has been reported as a manifestation of this reaction. Readministration of the drug causes recurrence of fever within 6 to 12 hours. The fever is thought to be related to hypersensitivity to the drug, although no antibodies have been shown.

TABLE 1.—*Types of Drug Fever*

Hypersensitivity
Altered thermoregulation
Pharmacologic action of a drug
Idiosyncratic susceptibility from a heritable biochemical defect
Administration related

TABLE 2.—*Drugs Causing Fever Due to Hypersensitivity Reaction*

Antibiotics
Penicillin, methicillin, sulfonamides
Streptomycin
Vancomycin
Tetracyclines
Nitrofurantoin
Demeclocycline hydrochloride
Phenytoin
Methyldopa
Antiarrhythmics, such as procainamide, quinidine
Isoniazid
Miscellaneous, such as clofibrate, allopurinol, nifedipine, ibuprofen, sulindac

Procainamide. Fever from procainamide develops after about two weeks and may be associated with a maculopapular rash, splenomegaly, arthralgias, malaise and eosinophilia, termed drug-induced lupus. A remittent fever of 39°C to 40°C (102°F to 104°F) may be seen. The fever subsides within 48 hours after the drug is withdrawn.

Quinidine. Fever from quinidine may appear as early as three days or as late as one year after the drug regimen is begun, but most reactions occur within 3 to 19 days. Fever is not dose-related and disappears within 14 to 48 hours after the drug is withdrawn. Leukocytosis or a pronounced left shift in leukocytes (or both), mimicking sepsis, has been reported with quinidine fever. The leukocyte count promptly returns to normal with discontinuation of the drug therapy.

Isoniazid. The incidence of drug fever with the use of isoniazid is low, reported in only 22 of 1,724 patients admitted to hospital. The incidence of fever increases with the use of several drugs. Fever occurs one to seven weeks after initiating the therapy. High fever associated with myalgias and repeated chills may simulate a septic process. Fever may appear after the first dose and may or may not be associated with hepatitis. Readministering the drug produces fever in two to three hours. Hypersensitivity to isoniazid may result in fever, rash, eosinophilia, Coombs-positive hemolytic anemia, vasculitis and meningoencephalitis.

Allopurinol. In about 10% of patients, untoward reactions develop with the use of allopurinol, mostly in the form of diarrhea, abdominal pain or skin rash. A few patients have severe reactions consisting of fever, eosinophilia, hepatic and renal dysfunction and severe dermatitis. Renal insufficiency and concomitant administration of thiazide diuretics predispose to hypersensitivity. There is evidence of diffuse immune-complex vasculitis in the form of immunoglobulin deposits in glomerular basement membranes and at the dermal-epidermal junctions of the skin.

2. *Altered Thermoregulation*

Fever from altered thermoregulation may be due to a direct effect on the central nervous system, as is seen with the use of amphetamines, cocaine and phenothiazines, or decreased heat loss due to vasoconstriction or decreased sweating, as is seen with atropine use. Monoamine oxidase inhibitors increase the catecholamine concentrations of tissues, resulting in a state of hypermetabolism and increased heat production. Excessive exogenous thyroid hormone can also cause fever by this mechanism. Another drug that can cause fever by this mechanism is cimetidine. In rare cases, fever has been reported to occur one to two weeks after the initiation of cimetidine therapy. The temperature can rise to 39.5°C (103°F) and readministering the drug causes fever within 12 hours. Cimetidine has been shown to cause fever by blocking histamine H_2 receptors in the thermoregulatory areas of the hypothalamus.

3. *Pharmacologic Action*

Fever due to the pharmacologic action of a drug is rare. The Herxheimer reaction follows by several hours the penicillin (or other) therapy given for spirochetal diseases. Patients present with high fever, chills, hypotension and leukocytosis, reaching maximum intensity in about eight hours. Recognizing this reaction in a patient with undiagnosed syphilis who is given an antibiotic for some unrelated

infection may be difficult. Fever associated with chemotherapy is due to the liberation of endogenous pyrogen resulting from rapid destruction of neoplastic cells.

4. Idiosyncratic Susceptibility

Idiosyncratic susceptibility from a heritable biochemical defect is shown by the syndrome of malignant hyperthermia of anesthesia, which is characterized by fever, tachycardia, arrhythmia, rhabdomyolysis, lactic acidosis and disseminated intravascular coagulation. Malignant hyperthermia has been linked to exposure to a variety of inhaled gases and has a high mortality. Of the patients in whom the syndrome develops, 50% have had prior anesthesia without recognized malignant hyperthermia. Patients at risk for this reaction may be identified by a history of previous anesthetic reactions or by a family history of adverse events during surgical procedures. Laboratory studies eliciting raised creatine kinase levels and abnormal contracture of skeletal muscle in response to caffeine and halothane are diagnostic of this disorder. Recommendations for prevention and treatment have been reviewed recently.

Idiosyncratic susceptibility from a heritable defect causing fever may be seen in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency in whom hemolysis develops due to a drug exposure. Fever in these patients is caused by release of endogenous pyrogens from erythrocytes. Drugs that cause hemolysis include primaquine phosphate, quinine, sulfonamides, quinidine and moth balls. Massive hemolysis may occur two to three days after these drugs are ingested. Heinz bodies may be seen in a peripheral smear. G6PD deficiency is most prevalent in black, Mediterranean and Southeast Asian populations.

5. Administration-Related Fever

Administration-related fever is caused by microorganism-produced exogenous pyrogens and injection-induced inflammation. The fever occurs during or shortly after the patient receives the medication and is usually related to septicemia from contaminated materials or thrombophlebitis caused by intravenous catheters and caustic drug solutions, including cephalothin, vancomycin hydrochloride and diazepam. Multiple intramuscular injections at the same site can cause the formation of a sterile abscess, resulting in release of endogenous pyrogens and the development of fever. Paraldehyde and pentazocine are agents that cause this latter phenomenon. Bleomycin and amphotericin B cause fever in a large percentage of patients by causing release of endogenous pyrogens from granulocytes. Fever with bleomycin ranges from 40°C to 42°C (104°F to 107.6°F) and is accompanied by rigors, hypotension and disseminated intravascular coagulation. Fever usually occurs after the first dose of bleomycin and is uncommon after subsequent injections.

Amphotericin B causes fever with chills in about 50% of patients who receive the drug intravenously for the first time. Fever appears one to two hours after the start of an intravenous infusion and subsides within four hours after its discontinuance. Fever may rise to as high as 40°C. The incidence of fever may decrease with continued therapy.

Diagnosis and Treatment

Drug fever should be suspected in any febrile patient receiving any medication, especially one of the commonly incriminated drugs. Drugs given on an as-needed basis or for diagnostic procedures should not be excluded. Drug fever related to the mode of administration is evident by the presence of local inflammation at the site of injection. Signs of superficial thrombophlebitis may be obvious when drugs are used intravenously. A hypersensitivity type of fever should be suspected when a patient appears well or when a fever, originally attributed to an underlying disease, persists or recurs despite apparent clinical improvement. Except the patient with methyldopa-related fever, who may appear quite ill, patients with drug fever generally appear well, without other symptoms or tachycardia, despite fevers as high as 40°C. This finding, in fact, is a major clue to the diagnosis of drug-related fever. Urticaria, skin rashes or eosinophilia, when present, are suggestive of a drug fever. Resolution of fever after withdrawal of a drug is strongly suggestive, but the recurrence of fever on reexposure is definitive evidence of a drug fever. A single therapeutic dose on rechallenge produces fever within a few hours, often to levels higher than previously observed. Readministering the offending drug may be dangerous, especially with methyldopa, because as many as 30% of severe drug reactions have been preceded by drug fever. Therefore, readministration is not recommended as a routine procedure, although it may be necessary in certain clinical situations.

Patients who are already febrile should not receive bleomycin until the fever is suppressed with antipyretic agents. The therapy for bleomycin-induced febrile reaction is supportive, directed toward lowering the body temperature and maintaining the blood pressure. Diphenhydramine and chlorpromazine have been given parenterally with success. This reaction may be prevented by giving a test dose and avoiding the drug in febrile patients. Adding 0.7 mg per kg of body weight of hydrocortisone may abolish or reduce chills in some but not all patients. A small test dose of amphotericin B (1 mg in 20 ml of 5% dextrose solution) should first be given intravenously over 10 to 30 minutes. If the patient manifests a severe reaction, such as fever, chills and hypotension, from the test dose, the second dose of amphotericin B should not exceed 5 to 10 mg and subsequent doses may be gradually increased to full dose. If after 5 to 15 minutes of discontinuation of amphotericin B infusion the patient continues to have severe chills and fever, an intravenous injection of 50 mg of meperidine hydrochloride will eliminate the symptoms.

When patients are receiving several drugs and hypersensitivity fever is suspected, all nonessential drug therapy should first be discontinued. Other essential drugs can be withdrawn, one at a time, every two to three days, if fever persists. The most likely drug thought to be causing the fever should be withdrawn first and, if possible, replaced with a chemically unrelated substitute. If a particular drug causing fever must be used, corticosteroids, but not antihistamines, suppress the fever and any other accompanying manifestations.

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