

Pattern of Drug Induced Fever in Two Cases

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Drug-induced fever is a symptom of an adverse drug reaction during administration of drugs intended to help a patient causes a hyper-metabolic state resulting in fever. There are also several side effects that are common to most antibiotics, regardless of class or drug. Fever is not an uncommon adverse effect due to antibiotics that confuse a physician in taking decision where to stop the drug or not. Reports on drug fever due to ciprofloxacin and azithromycin are rare. Here we will report two cases of drug fever with particular pattern due to ciprofloxacin and azithromycin.

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Introduction

Drug fever is defined as “a disorder characterized by fever coinciding with administration of a drug and disappearing after the discontinuation of the drug, when no other cause for the fever is evident after a careful physical examination and laboratory investigation”. Early diagnosis may reduce inappropriate and potentially harmful and expensive diagnostic and therapeutic interventions. However if clinician could assess a drug induce fever by observing its pattern due to a particular drug especially if it is an anti-microbial, without stopping the drug, it will be more helpful. The agents most commonly reported to be associated with causing fever include the penicillins, cephalosporins, antitubercular drugs, quinidine, procainamide, methyldopa, and phenytoin.¹ Report on drug fever due to ciprofloxacin and azithromycin are not common. Here we will discuss two cases of drug fever with particular pattern due to ciprofloxacin and azithromycin.

Case Report

Case-I

A male of 58 years old was suffering from febrile illness for the last three days. He complained difficulty in micturition and lower abdominal pain. His bowel was normal. On examination his oral temperature was 101.5°F. His appetite was good with clean moist tongue. All other physical findings were normal. His total leucocytes count (TLC) was 9,700/cumm of blood; neutrophil 62%, lymphocyte 31%, monocyte 04% and eosinophil 03%, haemoglobin level was 12.5 gram% and ESR 23 mm. Peripheral blood film for Malarial parasite was negative and dipstick test for malarial antigen (*Plasmodium vivax* and *Plasmodium falciparum*) was also negative. Routine urine examination revealed pus cell 30-40/HPF. Mid stream urine culture showed significant growth (2×10^6 /ml) of *Escherichia coli* which was sensitive to ciprofloxacin, ofloxacin and gentamycin. His serum bilirubin (0.7 mg/dl), ALT (21U/L) and fasting glucose level

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(4.5mmol/L) were normal. We started ciprofloxacin 500 mg bid dose orally. After two days of treatment his symptoms of UTI resolved but rise of body temperature continued. We repeated TLC, DLC and routine urine examination (pus cells 0-2/HPF) and found to be normal. From the third day onwards, we observed that, his pattern of rising temperature was different from previous illness (fig 1). It began to appear with intermittent double

rise of temperature in 24 hours synchronizing with the intake of ciprofloxacin. At this time morning temperature was normal and it began to rise gradually about one hour after the morning dose of ciprofloxacin and continued to rise to 101 °F at noon time and again declines to baseline in the afternoon. Again temperature rose one hour after the night dose and patient remained febrile till midnight.

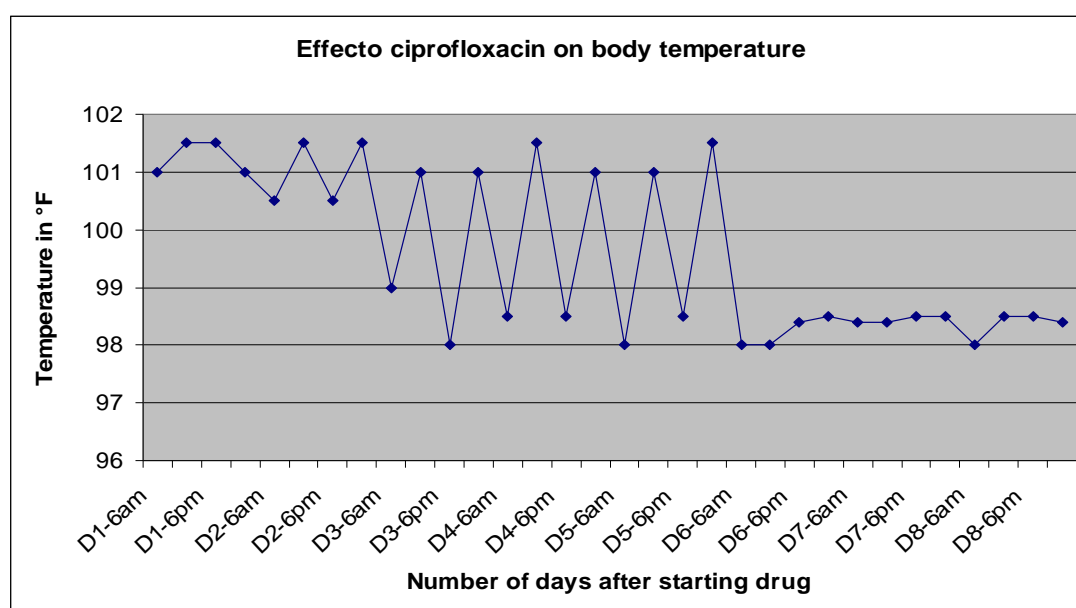


Figure 1. Pattern of temperature variation due to ciprofloxacin induced drug fever.

We observed for two days the same pattern of rising of temperature suggesting that it was due to ciprofloxacin. We stopped the drug and patient was cured and was afebrile for the next three weeks of follow-up.

Case-2

A young man aged 23 years suffering from febrile illness for the last 10 days. He complained severe weakness, headache and anorexia. Suspecting as a case of dengue (as the area was endemic zone) he was being treated with paracetamol only. His tongue was

found to be coated and dehydrated. Both flangs were tender. His morning body temperature was 103°F on the 11th day of illness and continuous. Routine blood examination showed TLC 10,500/cumm; neutrophil 52%, lymphocyte 43%, monocyte 04% and eosinophil 01%; haemoglobin level was 13.5gram%, ESR was 40mm. Routine urine test showed pus cell 0-2/HPF. Malarial parasite in peripheral blood film was not found and dipstick test for malarial antigen (*plasmodium vivax* and *plasmodium falciparum*) was negative. Dengue antibody

(both IgM and IgG) were negative. His serum bilirubin (0.8mg %), serum ALT (35 U/L) and fasting glucose level were normal. Serum electrolytes were within normal limit ($\text{Na}^+=136\text{mmol/l}$, $\text{K}^+=4.2\text{mmol/l}$, $\text{Cl}^-=99\text{mmol/l}$ and $\text{HCO}_3^-=27.5\text{mmol/l}$). Blood culture was done but showed no growth. His febrile agglutination tests were done. Result were: TO=1:320, TH=1:320, AH=1:80, BH=1:40; *Bricella abortus* =1:80, *Brucella me/itensis*=1:80; OX2, OXI9 and OX1 were 1:80, 1:80 and 1:40 respectively. Enteric fever was diagnosed and azithromycin was started orally with 1gm and 500 mg daily. Paracetamol also was given when temperature was above 102°F. After 72 hours of treatment patient's clinical condition was improving and his morning temperature gradually fell to 99°F on fourth day after treatment. But the patient remain febrile and temperature continue to rise gradually to 100°F after one hour after

taking azithromycin and continued to rise to 102°F at 10 am and 103 °F at 12am. He was given paracetamol at night. On the next morning his temperature was 98°F and clinical condition more improved. But temperature again rose to 99°F after one hour of the drug and gradually reached 101°F after another one hour and 103°F at 12am (Graph-02). After gaining three days' of same pattern of baseline body temperature in the morning, Widal test was repeated and titre was increased (TO-1:320, TH 1:640). Routine urine test done and was normal. Now, it was decided that this variation of temperature giving a uniform particular pattern of fever was due to azithromycin and not due to infection. We stopped the drug on the next day and there was no further rise of temperature from that day. Patient remained afebrile for next two weeks of follow up.

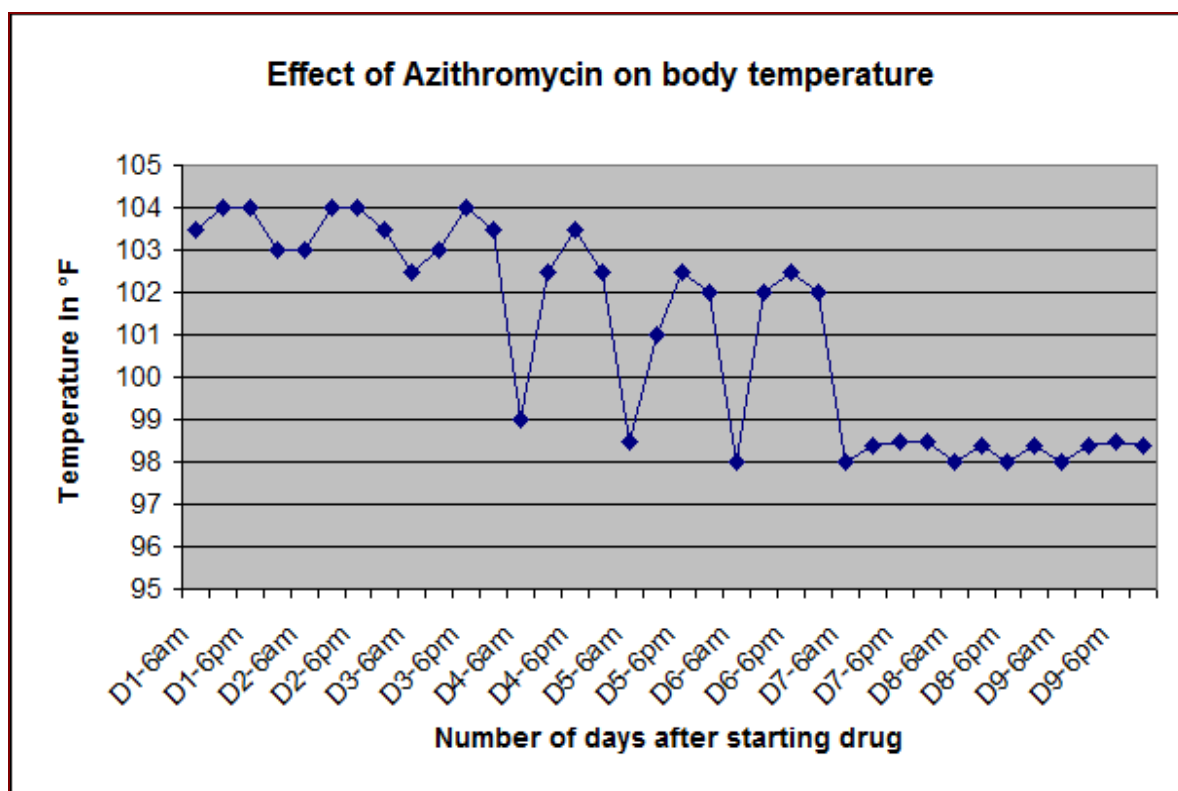


Figure 2. Pattern of temperature due to azithromycin induced drug fever.

Discussion

Clinicians are universally aware of the common occurrence of fever caused by drugs; although reliable data on incidence are not available, we reported another three cases on ciprofloxacin induced fever but azithromycin induced fever found not to be reported at the time of this writing. In all these cases, we found that drug fever is directly related with timing, dose and half life of antimicrobials. Half life of ciprofloxacin is short (4-6 hours), so its duration of induced fever is shorter and half life of azithromycin is long (11-14 hours) so induction period is longer. So, persistent of fever after clinical cure during treating an infective disease, idea of pattern of drug fever will help the physician to complete the course of antimicrobial avoiding further inappropriate expensive diagnostic and therapeutic interventions.

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