CASE PRESENTATION

CASE HISTORY

On 9/8/2010 a 27 year old Hispanic man was admitted to a psychiatric facility for treatment of undifferentiated schizophrenia. The patient received treatment with risperidone 3 mg daily. The patient’s psychiatric issues were well controlled and he tolerated the medication well.

On 12/02/2010 the patient developed a cough and was referred for a chest radiograph. The chest radiograph was abnormal and consistent with pulmonary tuberculosis. The patient had a history of a positive tuberculin skin test and QuantiFERON TB Gold In-Tube (QFT-GIT). Treatment for latent tuberculosis infection was not documented in the patient’s history. Sputum was collected and found to be acid fast bacilli (AFB) smear negative. Culture results were pending. The primary provider began treatment for latent tuberculosis infection (LTBI) on 12/02/2010 with 300 mg of isoniazid daily.

After initiation of LTBI treatment the patient’s cough continued and the patient developed fever and malaise. A repeat chest radiograph 12/13/10 revealed a thickening of the wall of the cavitary lesion. A bronchoalveolar lavage was performed on 12/14/10. The sample was Nucleic Acid Amplification test (NAAT) positive for Mycobacterium tuberculosis and later grew MTB.

The patient was started on standard antituberculosis therapy with a regimen that consisted of Rifampin, Isoniazid, Pyrazinamide and Ethambutol daily. Pyrazinamide was discontinued after 5 days due to symptomatic hepatoxicity. Isoniazid was discontinued 3 days later when INH resistance was reported. Moxifloxacin was added to strengthen the regimen.

Continued on next page
CASE HISTORY (continued)

The symptoms of pulmonary tuberculosis (cough, fever and malaise) subsided rapidly after the implementation of the multi-drug regimen. A repeat chest radiograph noted improvement. The patient converted to culture negative after 2 weeks of therapy.

After initiation of TB treatment the patient began to exhibit psychiatric symptoms. He became reclusive and spent extended periods of time in his darkened room, rarely interacting with the staff and other patients. The patient also noted the re-emergence of auditory hallucinations. A drug-drug interaction between risperidone and rifampin was identified. A pharmacist and psychiatrist were consulted. Following the consultation, the risperidone dosage was increased. The psychiatric symptoms improved as a result of the dosage adjustment.

DRUG INTERACTION OVERVIEW

Risperidone is an atypical anti-psychotic that is widely used to treat psychosis associated with schizophrenia, bi-polar disorder and a variety of other psychiatric conditions. It is a potent antagonist for 5-HT₂ receptors and Dopamine D2 receptors. It is effective in reducing both the positive symptoms (symptoms that reflect an excess or distortion of normal functions, i.e. auditory hallucinations) and negative symptoms (symptoms that reflect a suppression or absence of normal function, i.e. catatonic state) of schizophrenia.

Risperidone displays a high interindividual variability in treatment responses. This variability is thought to be due to pathophysiological, environmental, genetic factors and a variety of other factors. One consistent factor that contributes to the differences in treatment effectiveness is the variability of drug metabolism. Risperidone is mainly metabolized in the liver by the polymorphic cytochrome enzyme P450 2D6. Recent studies have indicated the involvement of the cytochrome P3A4 enzyme in the metabolism of risperidone and cytochrome P3A4 in the small intestine (1, 2).

Rifampin (rifampicin) is a semi-synthetic derivative of the bacteria: Amycolatopsis mediterranei. Rifampin is a member of the rifamycin class of antibiotics. It is considered to be the most potent and important antituberculosis drug. Rifampin is a potent inducer of the hepatic and intestinal cytochrome P3A4 enzyme. As a result rifampin reduces the plasma concentration which decreases the therapeutic effects of risperidone (1, 2). When dealing with a patient who is receiving risperidone and rifampin concurrently, adjusting the risperidone dosage may be required to reach therapeutic effect.

Rifabutin is another member of the rifamycin class of antibiotics; it is similar to rifampin in many aspects including a similar mechanism of action. Rifabutin is also an inducer of the p450 enzyme system but its induction is much less potent than that of rifampin and consequently it has less effect on the metabolism and therapeutic effect of other medications. TB patients being treated for other medical or psychiatric conditions may benefit from substitution of rifabutin for rifampin if significant drug-drug interactions involving rifampin and the patient’s other medications are present.

CLINICAL IMPLICATIONS OF INTERACTION

In a recent study published in the Journal of Clinical Pharmacology (2) healthy volunteers received co-administered rifampin and risperidone. Rifampin considerably decreased the plasma concentration of risperidone. This may result in the re-emergence of previously controlled psychiatric symptoms. These include but are not limited too:

- Auditory Hallucinations
- Apathy
- Social Withdrawal
- Delusions
- Disorganized speech and behavior
- Neurocognitive deficits (eg. memory loss, loss of cognitive abilities)

Adequate treatment of psychiatric illness is essential for maximizing the quality of life of an individual. TB patients with well-controlled psychiatric illness have better adherence to TB medications and therefore better TB treatment outcomes.
DIFFERENTIATING BETWEEN ACTIVE TUBERCULOSIS AND LTBI

Correct management of the TST or IGRA positive person depends on making the correct diagnosis. Active TB disease must always be excluded before a diagnosis of LTBI can be made and treatment of LTBI initiated. Evaluation of those with a positive TST or IGRA includes a medical assessment and a CXR. Persons with LTBI have no evidence of active disease on CXR and have no symptoms; they are not infectious. Some individuals are at risk of progression to active TB without treatment of their LTBI. The following factors are known to increase the risk of progression from LTBI to active disease:

- Recent contact with an infectious TB case
- Substance abuse
- Low BMI
- Diabetes mellitus
- Recent immigration
- Chronic renal failure

Patients with active pulmonary TB disease are generally infectious and pose a public health risk. Those with an abnormal CXR or symptoms should be identified as TB suspects and have sputum examined for AFB smear and culture. If the smear is positive, the individual is coughing, or the CXR is suggestive of active TB disease, treatment with the standard four drug regimen of INH, rifampin, ethambutol, and PZA should be started pending the results of the sputum culture. If the diagnosis of TB disease is less likely, the smears are negative and the individual is not coughing, the person can be observed and treatment can be held pending the results of the cultures. Whenever a decision is made to initiate treatment before the culture report is final, treatment should be with the four drug regimen. Treatment of active disease with a single drug may lead to acquisition of drug resistance.

TEACHING POINTS

1. Treatment for Latent Tuberculosis infection (LTBI) should not be initiated until active disease has unequivocally been ruled out. Not doing so and treating active TB Disease with one drug may lead to the development of drug resistance.

2. Untreated mental illness places patients at high risk for treatment failure. Poorly controlled disease places patients at risk for poor adherence to therapy and decrease the chances of successful cure.

3. When a patient is on a variety of medications (and there is high probability of multiple drug–drug interactions) rifabutin should be considered as a substitute for rifampin. Rifabutin has considerably less potent interactions than rifampin (e.g. when a patient is receiving protease inhibitors as part of an HIV treatment regimen).

4. When a patient is being treated concurrently with rifampin and risperidone, the dosage of risperidone may have to be adjusted to achieve therapeutic levels. The dosage of risperidone will also need to be re-adjusted after the discontinuation of rifampin treatment. Risperidone dosage will usually need to be decreased ten to fourteen days following the discontinuation of rifampin to avoid the development of adverse effects as a result of high risperidone serum levels.

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REFERENCES

REFERENCES (continued from previous page)


TB LINKS

TB Education and Training Network
http://www.cdc.gov/tb/education/Tbetn/default.htm

Find TB Resources
www.findtbresources.org

Tuberculosis Epidemiologic Studies Consortium (TBESC)
http://www.cdc.gov/tb/topic/research/TBESC/default.htm

Regional Training and Medical Consultation Centers’ TB Training and Education Products – (Joint RTMCC Products Page)
https://sntc.medicine.ufl.edu/rtmccproducts.aspx

Program Collaboration and Service Integration (PSGI)
http://www.cdc.gov/nchhstp/programintegration/Default.htm

****If your organization has any additional links for TB resources you would like published, please send them to Alysia.gibbons@uthsc.edu****