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Research Article

Tuberculosis – Real Challenge for Anesthetist in Developing Country

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Abstract: Tuberculosis is a common problem in developing countries and provides a number of challenges for the anaesthetist. Patients may present in a variety of ways. Constitutional and pulmonary symptoms are the most common. These may impact on fitness for surgery and choice of anaesthesia. Tuberculosis treatment has the potential for a number of significant drug interactions. These are primarily mediated through induction of the cytochrome P450 enzyme system by rifampicin. Guidelines for the prevention of tuberculosis in the theatre environment need to be followed to avoid placing staff and other patients in danger.

Keywords: Tuberculosis, Immunodeficiency, antitubercular drug, drug interactions.

INTRODUCTION

Tuberculosis is a common problem, especially in the developing world. Incidence of TB is high in developing countries e.g. In India its 199 per 100000 as per recent data. This means huge amount of the population develops tuberculosis every year. Many will be coinfected with human immunodeficiency virus (HIV). Even in the developed world, concerns have been raised about the impact of immigration on the transmission of tuberculosis. There has been a marked increase in the number of tuberculosis cases, which has paralleled the emergence of HIV. Despite high cure rates obtained by following a full six month course of antibiotic therapy, the problem of resistance is starting to emerge. Many cases are multi-drug resistant (MDR), defined as resistance to rifampicin and isoniazid and extensively drug-resistant (XDR) tuberculosis were diagnosed. By definition, XDR tuberculosis possesses additional resistance to a fluroquinolone and any second-line injectable drugs, e.g. amikacin.

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PATHOPHYSIOLOGY

Mycobacterium tuberculosis spread via the airborne transmission of small droplets (0.5-5 μm). Because of its high oxygen tension, the primary site of infection is the upper lobe of the lung, forming the Ghon focus. Bacteria invade and replicate within macrophages. This is followed by a T cell-mediated response, which walls off the infected cells to form a granuloma. Bacteria within the granuloma can become dormant, resulting in latent infection. At this stage, the patient will be asymptomatic, but may show a positive response to a tuberculin skin test. Factors that increase the likelihood of progression to active disease include time from exposure (most common in the first year), the age of the patient (younger than five years old), and the competency of the immune system.

SYMPTOMS

Patients may present in a number of ways:

- Pulmonary disease is the most common presentation, with a chronic productive cough and haemoptysis. Enlargement of the lymph nodes can cause bronchial compression with localised wheeze, while haematogenous spread can lead to widespread lung infection, known as miliary tuberculosis.
- Constitutional symptoms secondary to the production of proinflammatory cytokines are

commonly seen. These include fever, night sweats, loss of weight, or failure to thrive in children.

- Hypersensitivity phenomena may occur following activation of T cell-mediated immunity. These include conditions such as erythema nodosum, phlyctenular conjunctivitis and Poncet's disease.
- Extrapulmonary disease can manifest as infection of almost any organ. Common examples include lymphadenitis (scrofula), bones and joints, abdominal tuberculosis and meningitis.

DIAGNOSIS

Traditionally, diagnosis is made by visualising acid-fast bacilli on sputum.

Newer technology, such as the Xpert® M. tuberculosis/resistance to rifampicin or GeneXpert®, make use of real-time polymerase chain reaction to detect specific DNA sequences. They can provide much quicker results (within two hours), as well as information on rifampicin resistance.

T cell interferon-γ (IFN-γ) release assays, which measure the number of IFN-γ-secreting T cells, have been developed as an alternative immune-based approach to the tuberculin skin test to detect infection.

TREATMENT IMPLICATIONS IN ANESTHESIA

The cornerstone of treatment is directly observed treatment (DOT) for at least six months. First-line treatment includes rifampicin, isoniazid (INH), ethambutol and pyrazinamide, given according to guidelines for new cases, retreatment, and children younger than eight years of age. Fixed-dose combinations help to reduce the pill burden. Steroids are given for six weeks in cases of tuberculosis meningitis, pericarditis and airway obstruction from lymph node compression. Tuberculosis treatment has the potential for serious side effects, some of which may impact on the anaesthetist. Rifampicin can cause thrombocytopaenia when given in high doses. INH may cause sensory neuropathy, which should be ascertained clinically before performing regional nerve blocks. This complication can be prevented by adding pyridoxine (vitamin B6) in high-risk cases. Ethambutol has the potential to cause optic neuritis. Drug-induced hepatitis (DIH) is a worrying complication. When tuberculosis treatment is combined with concomitant antiretroviral therapy, a mild elevation in liver enzymes is common. DIH requires immediate halting of tuberculosis drugs, with careful re-introduction under specialist care. Wherever possible, surgery should be avoided during this period. MDR and XDR tuberculosis require extended treatment for up to two years with four or five drugs, depending on resistance patterns.

ANESTHETIC IMPLICATIONS OF TUBERCULOSIS

The anaesthetist may be presented with a patient with tuberculosis in a number of scenarios. Procedures such as lymph node biopsies and bronchoscopies may be required to obtain a definitive diagnosis. Patients may require surgery for tuberculosis complications, such as hydrocephalus and intestinal obstruction. Lastly, patients requiring elective or emergency surgery may have active tuberculosis incidentally, or be on antituberculous therapy. There are three major implications for the anaethetist:

- The general state of the patient's health and the impact of the disease on organ function.
- The treatment that the patient is receiving and the considerable potential for drug interactions.
- The risk of transmission of tuberculosis to staff and other patients.

Patient assessment is very important , the patient may be acutely ill, either with tuberculosis or a superadded infection. Chronic lung disease with bronchiectasis and fibrosis develops as a result of long-standing tuberculosis. A full history, examination and relevant investigations are needed, as dictated by the clinical condition of the patient, to determine the extent of organ dysfunction.

DRUG INTERACTIONS

Drugs used for the treatment of tuberculosis probably have the greatest impact on the anaesthesia. Drug interactions are mostly due to pharmacokinetic changes following the induction of liver enzymes. Rifampicin is responsible for most observed drug interactions. It is a potent inducer of the cytochrome P450 system, especially isoenzyme 3A4, which is involved in the metabolism of nearly 50% of drugs. This can result in increased metabolism, and therefore subtherapeutic effects, or the increased production of toxic metabolites. CYP3A4 is also found in the small intestine. For this reason, oral drugs are more affected than those given intravenously. On the other hand, INH is a CYP450 inhibitor. However, due to differential effect on specific isoenzymes, these two drugs do not simply cancel each other out. The potential for a drug interaction is further compounded when a patient is also taking antiretroviral treatment, and specifically protease inhibitors. The extent of this problem was demonstrated by Backman, Olkkola and Neuvonen. Oral midazolam was given to healthy volunteers following five days of pretreatment with either rifampicin or placebo. They showed a 96% reduction in area-under-concentration time curve and a 94% reduction in maximum concentration in the rifampicin group. They concluded that "orally administered midazolam is ineffective during rifampin treatment". This has obvious

implications for the use of oral midazolam as anxiolytic premedication in patients on antituberculous therapy.

Induction Agents:

Recovery from the effect of intravenous induction agents is primarily due to redistribution. TB therapy is unlikely to have an effect on a single induction dose. However increased metabolism may be important in total intravenous anaesthesia, with a greater potential for awareness. While there is no evidence to support this, one should be mindful of this risk and consider the use of depth of anaesthesia monitoring in these patients.

Local Anesthetics:

As they exert their action primarily at the site of injection, local anaesthetic drugs are still likely to be effective, and help to avoid many of the other drug interactions seen with opiates. Increased metabolism may result in a decreased risk of local anaesthetic toxicity.

Volatile Anesthetics:

Halothane is metabolised via isoenzyme CYP2E1 to trifluroacetic acid. This molecule has the potential to act as a hapten to trigger an immune mediated hepatitis. CYP2E1 is induced by INH. Thus patients on antituberculous therapy are potentially at increased risk of halothane hepatitis. The minimal metabolism of the newer volatile agents makes them a better choice.

Neuromuscluar blocking drugs:

Liver dysfunction results in decreased pseudocholinesterase levels which effect suxamethonium metabiolism. Similarly cisatracurium (organ independent metabolism) and pancuronium (renal excretion) are minimally affected by tuberculosis therapy. While no trials specifically look at interactions with TB treatment, it has been shown that the effect of vecuronium is prolonged by cimetidine, an enzyme inhibitor, and shortened by phenytoin enzyme induction. Rocuronium is less affected but resistance to muscle blockade has been shown with carbamazepine. Streptomycin may potentiate the effects of non-depolarising agents. Non-depolarising neuromuscular blocking drugs should, therefore, be titrated to response, with frequent evaluation using a nerve stimulator.

Analgesics:

While the metabolism of morphine predominantly involves phase II reactions via UDP-glucuronosyltransferases, antituberculous therapy seems to have an effect. A loss of analgesic effect of oral morphine has been demonstrated following pretreatment with rifampicin.Fentanyl and alfentanil are both extensively metabolised by CYP450 3A4 therefore, also show the potential for a shortened duration of action. The analgesic effect of codeine is mediated through its metabolism to morphine via CYP450 2D6. One may, therefore, expect a greater analgesic effect following enzyme induction. However, it is also metabolised to inactive norcodeine via isoenzyme 3A4, resulting in an overall decreased effect.The effect of tramadol is unchanged. Of the non-steroidal anti-inflammatory drugs, the effect of diclofenac is decreased with rifampicin, while that of ibuprofen is unchanged, making it a safer option. Analgesia should therefore be titrated to effect with the potential to require more frequent dosing.

CONCLUSION

Tuberculosis is a common problem, especially with the rise of HIV. It has significant implications for the anaesthetist. The potential for drug interactions is most concerning. The transmission of tuberculosis to other patients, theatre staff and anaesthesiologists is a potential danger, and active measures should be taken to prevent this.

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