Tuberculosis: the implications for anaesthesia

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Keywords: tuberculosis, antitubercular agents, drug interactions, transmission, bacterial filter

Abstract

Tuberculosis is a common problem in South Africa, 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.

℗ Peer reviewed. (Submitted: 2013-05-24. Accepted: 2013-10-22.) © SASA South Afr J Anaesth Analg 2013;19(6):301-305

Introduction

Tuberculosis is a common problem, especially in the developing world. In 2010, the World Health Organization estimated 8.8 million new cases worldwide.[1] South Africa is one of the epicentres of the epidemic, with an incidence of 971 per 100 000. This means that almost one per cent of the population develops tuberculosis every year. Fifteen per cent of these are children and two thirds will be co-infected with human immunodeficiency virus (HIV). Even in the developed world, concerns have been raised about the impact of immigration on the transmission of tuberculosis.[2]

There has been a marked increase in the number of tuberculosis cases, which has paralleled the emergence of HIV. This increase can be explained by the fact that the lifetime risk of an immunocompetent patient who is infected with tuberculosis, progressing to develop active disease, is 10%. This rises to 5-8% per year in a patient with HIV.[3]

Despite high cure rates obtained by following a full six-month course of antibiotic therapy, the problem of resistance is starting to emerge. 1.8% of new cases and 6.7% of retreatment cases in South Africa are multi-drug resistant (MDR), defined as resistance to rifampicin and isoniazid.[4] In 2009, almost 600 cases of 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. Most cases of MDR tuberculosis and XDR tuberculosis in South Africa have been detected in the Western Cape, the Eastern Cape and KwaZulu-Natal (Table I).[5]

Table I: The incidence of multidrug-resistant and extensively drug-resistant tuberculosis by province in 2009[5]

Province	Number of cases of multidrug-resistant tuberculosis	Number of cases of extensively drug-resistant tuberculosis
Eastern Cape	1 858	123
Free State	253	3
Gauteng	1 307	65
KwaZulu-Natal	1 773	254
Limpopo	204	6
Mpulmalanga	446	18
North West	520	13
Northern Cape	631	40
Western Cape	2 078	72

As anaesthetists, we will certainly be faced with this disease and the associated implications for patient health, as well as the potential for drug-drug interactions.

Pathophysiology

Mycobacterium tuberculosis is spread via the airborne transmission of small droplets (0.5-5 µm). Usually, infection

occurs between household contacts with prolonged contact. However, exposure to only a few bacteria is needed to establish infection. 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.[6]

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.[7]

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.[8]

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.[9]

Obtaining a sputum sample can be difficult in children, and the diagnosis is usually made on the basis of signs and symptoms of tuberculosis, positive contact and a positive tuberculin skin test (Mantoux®).[8] Gastric aspirates can be used, but have a pick-up rate of less than 40%.[10] 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.[11]

Treatment

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.[12] 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.[7]

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 B_6) in high-risk cases. Ethambutol has the potential to cause optic neuritis. For this reason, it is not routinely given to children.

Drug-induced hepatitis is a worrying complication. When tuberculosis treatment is combined with concomitant antiretroviral therapy, a mild elevation in liver enzymes is common. However, symptomatic hepatitis has a mortality of almost 5%,[13] and 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. Besides the added cost of treatment, there is also an increased risk of life-threatening side-effects.

Anaesthetic implications

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

The patient may be acutely ill, either with tuberculosis or a superadded infection. Alternately, he or she may be

chronically ill, malnourished and frequently anaemic. 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 anaesthetist. 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.[14] 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.

Swart and Harris reviewed the effects of antituberculous therapy on a number of drugs and is an excellent reference.[15] This article will focus only on those drugs that relate to anaesthesia. Few studies have been conducted specifically that have examined anaesthetic agents and tuberculosis therapy. Most available information is deduced from studies with other known enzyme inducers or inhibitors.

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 Anaesthetics

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 anaesthetics

Halothane is metabolised via isoenzyme CYP2E1 to trifluro-acetic 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.[16] The minimal metabolism of the newer volatile agents makes them a better choice.

Neuromuscluar blocking drugs

Unless liver dysfunction results in decreased pseudo-cholinesterase levels, the effect of suxamethomium is unchanged. 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.[17] Rocuronium is less affected but resistance to muscle blockade has been shown with carbamazepine.[18] 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.[19] Fentanyl and alfentanil are both extensively metabolised by CYP450 3A4, therefore, also show the potential for a shortened duration of action.

The metabolism of codeine is interesting. 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.[15] 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.[15] Analgesia should therefore be titrated to effect with the potential to require more frequent dosing.

Table II: A summary of the effect of tuberculosis treatment on various anaesthetic agents

Drug class	Effect of tuberculosis treatment	Recommendation
Induction agents	Unchanged	Beware risk of awareness with total intravenous anaesthesia
Volatile agents	An increased risk of halothane hepatitis	Newer agents are preferable
Local anaesthetics	Unchanged	Useful to avoid general anaesthetic and opioids
Muscle relaxants	Increased metabolism of rocuronium and vecuronium	Titrate and monitor response using nerve stimulator
Opiates	Increased metabolism, often requiring more frequent dosing	Titrate to effect The use of regional techniques and patient-controlled analgesia is recommended

Table II details the effect of tuberculosis treatment on various anaesthestic agents.

Therefore, the choice of anaesthetic depends on the patient, the procedure and the severity of the disease. Regional anaesthesia is often preferred in patients with chronic lung disease and to avoid potential drug interactions. However, this is not possible in many cases. Drugs should be tailored to the expected drug interaction and monitored for effect. Hepatotoxic drugs must be avoided.

Spread of tuberculosis

The spread of tuberculosis to other patients (many of whom are immunocompromised) and to theatre staff is an area of concern. Because of the close proximity of the patient's airway during intubation, anaesthetists are at particular risk.[20] Children are less likely to have cavitary disease and are, therefore, less infectious.[7]



Figure I: Example of an N95® mask

In 2005, the American Society of Anesthesiologists (ASA) produced guidelines relating to the perioperative management of patients with active tuberculosis.[21] Elective surgery should be delayed until the patient is no longer infectious. The ASA defines this as having been on treatment for 2-3 weeks, clinically getting better, and having had three negative sputa on different days. While practically, the third criterion might be difficult to achieve, the first two should certainly be followed.

Elective cases should be booked as the last case of the day to allow decontamination of the theatre following the case. The patient should be transferred wearing an N95® mask. He or she should be brought straight to theatre, rather than wait in a central holding area where exposure to other patients could occur. Traffic inside the theatre should be minimised to essential staff. Theatre staff must wear N95® masks. This is especially true for high-risk procedures, such as intubation and bronchoscopy. The anaesthetist should ensure adequate anaesthesia and muscle relaxation to ensure that the patient does not cough on intubation.

Unless gas flows are stopped for longer than one hour between cases, *M. tuberculosis* has been shown to be able to pass through the anaesthetic machine.[22] The presence of a soda lime canister does not guarantee eradication, as desiccated soda lime is not bactericidal. Therefore, it is recommended that a bacterial filter is placed both by the patient's airway and on the expiratory limb of the circuit. These should be able to filter more than 99.97% of particles greater than 0.3 µm. While not specifically advocated by ASA, it would be good practice to sterilise the circuits after such a case.

Ideally, the patients should be recovered in a private room, rather than in the central recovery area. Practically, this may mean that he or she will need to recover in theatre before going back to the ward directly. The N95® mask should be placed back on as soon as active airway management is no longer required. However, these masks increase airway flow resistance by approximately 120%.[23] A large venture-type face mask can be placed over the N95® mask to provide supplemental oxygenation. The N95® should not be worn by the patient if he or she is hypoxic or in respiratory distress. Similary, if hypoxia or respiratory distress occurs while wearing the mask, it should be removed.

Skin testing programmes for at-risk staff have been advocated by ASA, as well as in the most recent National Institute for Clinical Excellence guidelines.[24] Staff members who receive a positive tuberculin skin test are prescribed INH for 6-9 months. This has been shown to prevent progression to active disease.[25] The confounding effects of previous BCG immunisation and poor compliance with INH therapy hampers these programmes.

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.

Declaration

There was no external funding.

Conflict of interest

No competing interests are declared.

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