Poor adherence not enough to cause development of MDR-TB

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Poor adherence may not be enough to cause multidrug-resistant tuberculosis, a laboratory study published in the online edition of the *Journal of Infectious Diseases* suggests.

Moreover, the failure of tuberculosis (TB) therapy only occurred at extremely high levels of non-adherence.

A mathematical model also suggested that approximately 1% of patients taking TB treatment would develop multidrug-resistant TB (MDR-TB), even with perfect adherence. The investigators believe that this is due to differences in the way drugs are processed between individual patients, meaning that some individuals do not have therapeutic levels of anti-TB drugs in their blood.

'We propose pharmacokinetic variability as a working hypothesis for the emergence of MDR-TB,' comment the authors. 'If proven to be correct, this problem lends itself to a scientific solution of either optimizing doses … by taking into account pharmacokinetic variability or, better still, individualisation of each patient's doses if resources are available.'

TB is usually treated with a four-drug regimen consisting of isoniazid, rifampicin, ethambutol and pyrazinamide. In many settings it is provided as directly observed therapy (DOTS).

However, TB can develop resistance to the drugs used in its treatment. TB with resistance to isoniazid and rifampin is called multidrug-resistant, or MDR-TB.

Poor patient adherence is thought to be the main factor associated with emergence of MDR-TB. However, the level of adherence associated with the development of MDR-TB is unknown.

Conducting a clinical trial in patients to establish the relationship between adherence levels and development of MDR-TB would be highly unethical. Therefore investigators designed a laboratory study assessing the efficacy of standard-dose TB therapy administered daily for between 28 and 56 days at different levels of patient adherence.

They also ran a computer simulation that examined the effect of individual patient pharmacokinetics on the emergence of multidrug-resistant strains of TB. This was based on a population of 10 000 patients with drug-susceptible TB in Cape Town, South Africa.

'We hypothesized that low drug concentrations encountered due to pharmacokinetic variability lead to effective monotherapy and hence drug resistance in a portion of patients,' write the investigators.

The impact of adherence on both the bactericidal effect of therapy (the killing of rapidly multiplying bacteria by antibiotics) and the sterilising effect of treatment (the killing of semi-dormant or slowing replicating bacteria) were assessed.

Adherence levels of between 100% and 60% were found to have broadly similar bactericidal efficacy over 28 days. An adherence level of 40% was associated with slower bacterial kill rates until day 14. Treatment completely failed with an adherence level of 20%.

'The breakpoint of non-adherence was 60% - 80% of doses of the daily regimen.'

Approximately 4% of bacteria in the experiment were resistant to pyrazinamide. However, this fell to just 1% after 14 days, leading the researchers to comment: 'non-adherence did not amplify the pyrazinamide-resistant populations'.

Nor did TB develop resistance to either isoniazid or rifampicin, even at adherence levels leading to the failure of therapy.

Tests were then carried out examining the sterilising effect of different levels of adherence. Missing 70% of doses was associated with a slower kill rate and missing 80% of doses led to the failure of therapy. Neither isoniazid nor rifampicin-resistant bacteria emerged at any adherence level.

Many DOTS programmes provide therapy during the five days of the working week, with a two-day break at the weekend. The investigators calculated that dosing pattern equates to taking 71% of doses, well above the level needed for therapy to work.

However, if the DOTS programme relied on thrice-weekly treatment, 'practically any nonadherence leads to therapeutic failure,' write the authors. 'Thus, it should be questioned whether it is wise to recommend this regimen.'

The investigators then ran their computer simulation to assess the role of pharmacokinetics on the development of MDR-TB.

Its results showed that approximately 60% of patients would have no TB in their sputum 2 months after starting therapy – a similar response rate seen in DOTS programmes.

However, the individual pharmacokinetic profiles of patients meant that even with 100% adherence, approximately 1% of patients would develop MDR-TB within 8 weeks of starting therapy.

'No MDR-TB emerged with non-adherence in repeated experiments,' conclude the investigators, who 'propose pharmacokinetic variability as a more likely cause of MDR-TB emergence'.

In an accompanying editorial Dr Veronique Dartois praised the 'elegant *in vitro* model' used by the investigators, and believes their findings 'constitute the starting hypothesis for future animal studies'.

Monitoring drug levels could, she believes, be as important as checking adherence.

Srivastava S, et al. Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. J Infect Dis, online edition: doi:10.1093/infdis/jir658, 2011.

Dartois V. Drug forgiveness and interpatient pharmacokinetic variability in tuberculosis. J Infect Dis, online edition: doi:10.1093/infdis/jir662, 2011

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