THE MANAGEMENT AND CONTROL OF TUBERCULOSIS IN MALTA

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Introduction

Tuberculosis is a chronic disease caused by *Mycobacterium tuberculosis*. The disease occurs throughout the world and remains an important cause of morbidity and mortality in many developing countries. Each year, it is estimated that 8 million new cases occur and that it causes three million deaths. Whereas its prevalence has declined considerably in the industrial world within the last 50 years, it has re-emerged among patients with human immunodeficiency virus.

The use of chemotherapy has contributed generously to the rapid decline in tuberculosis mortality occurring in the last four decades. The use of chemotherapy in non-compliant patients has been successful to a much lesser extent. Fixed-dose combination products have been formulated to minimize the compliance required for the patient to adhere to the treatment regimen. The quality control and bioavailability of fixed dose combination preparations has recently been disputed.

Three studies were performed in order to:

Study A

Analyse the local behaviour of tuberculosis since it became a notifiable disease by legislation in 1908; and study the impact of chemotherapy on the epidemiology of tuberculosis in Malta.

Study B

Assess the compliance with prescribed treatment regimens among tuberculosis patients.

Study C

Perform and compare the in vitro dissolution profile of a locally manufactured generic preparation of Rifampicin 300mg and Isoniazid 150mg tablets to that of Rimactazid 300 tablets and to compare the rates of release of rifampicin from these formulations with the release of rifampicin from Rimactane 300 capsules.

Methodology

Study A

Epidemiology

Descriptive epidemiology of tuberculosis in Malta was based on data obtained mainly from the National Tuberculosis Register, Tuberculosis Annual Reports, Vital Statistics, WHO and local publications. The advances made in the management and control of tuberculosis throughout the latter half of this century were reviewed.

Study B

Patient Interviews

Interviews were conducted with 11 diagnosed tuberculosis out-patients attending the chest clinic at St Luke's Hospital, either for treatment or as follow-up cases, during the period November-December 1991. The patients' histories were analysed before each interview.

Study C

Dissolution Testing

The apparatus used to dissolve the tablets/capsules complied with the requirements as specified in the BP 1988, Appendix XII D, Apparatus I. The test method for the dissolution of rifampicin and isoniazid tablets was a validated method obtained from 'International Dispensary Association' laboratory (Netherlands). The test method for the dissolution of rifampicin capsules was the one suggested in the USP XXII.

Results

Study A

Epidemiology

Since 1910 with the exception of two peaks in 1918 and 1942, the tuberculosis notification rate has declined rapidly to the present low level of 3.0 per 100,000 population. The tuberculosis mortality rate has followed the same pattern but at a lower level. Table 1 shows a dramatic

fall in tuberculosis mortality rate occurring in the 1950's. This coincides with the introduction of isoniazid and other drugs of choice in the treatment of tuberculosis.

Table 1: Mortality per year per 100,000 population

Period	No of Deaths from pulmonary TB	Rates /100,000	% of previous rate
1910-1919	2,080	193.0	
1920-1929	1,501	66.1	34.2
1930-1939	1,306	51.1	77.3
1940-1949	1,506	52.5	102.7
1950-1959	412	13.1	25.0
1960-1969	101	3.2	24.4
1970-1979	14	0.5	15.6
1980-1989	8	0.2	40.0

The infectivity rate, as determined by tuberculin sensitivity testing, in 1987, was estimated at 2.5% as opposed to 33.12% in 1950.

Study B

Patient Interviews

Interviews showed that:

i) 65% (n=7) were ready to communicate problems related to their condition to the pharmacist;

ii) the majority of all patients had a fair knowledge on the disease/treatment regimen and wanted to know more;

iii) all the patients (n=11) claimed to be taking the medication as prescribed by the medical officer in charge and attended the chest clinic regularly;

v) at least 36.3% (n=4) were not informed about the possible side-effects of certain drugs.

Study C

Dissolution testing

Table 2: Percentage content dissolved at various time intervals of the 3 formulations subjected to dissolution testing.

Time lapse (mins)	Percentage content dissolved				
	A		B		C
	Rifampicin	Isoniazid	Rifampicin	Isoniazid	Rifampicin
15.0	90.96%	78.9%	81.00%	84.48%	90.96%
30.0	97.89%	87.12%	85.44%	88.80%	93.90%
45.0	99.90%	93.12%	91.26%	95.04%	93.45%

A = Rimactizid 300 tabs
B = Rifampicin 300mg + Isoniazid 150mg tabs
C = Rimactane 300 caps

Table 3: Statistical analysis by student's t-test of above results

Formulations	t-values at various time intervals (P>0.05)		
	15 min	30 min	45 min
A vs B (n=11) (Rifampicin)	t_c = 2.262 t_c= 12.877	t_o = 2.262 t_c = 16.794	t_o = 2.2620 t_c = 5.0933
A vs C (n=12) (Rifampicin)	t_c = 2.228 t_o = 0.000	t_o = 2.2280 t_c = 5.2253	t_o = 2.2280 t_c = 4.2562
B vs C (n=11) (Rifampicin)	t_o = 2.2620 t_c = 9.5697	t_c = 2.2620 t_c =17.6300	t_o = 2.2620 t_c = 3.2704
A vs B (n=11) (Isoniazid)	t_o = 2.2620 t_c = 4.8487	t_o = 2.2620 t_c = 1.4569	t_o = 2.2620 t_c = 1.5557

t_o = $t_{tabulated}$ t_c = $t_{calculated}$

Discussion

The incidence of tuberculosis in Malta as reflected by the notification rates compare more than favourably with that of other countries. The mortality rate can no longer be used as a yardstick in assessing the situation because of the great reduction in the case fatality rate. The estimated 2% tuberculin positivity that prevailed during the 1990's is very close to the 1% required by the World Health Organisation Standards.

Hospital pharmacists can increase patient compliance when a prescription is collected, counselling being their major tool in the process. It should be recognised that obeying instructions is not the problem, rather understanding and being motivated to comply.

With respect to Isoniazid, the dissolution profile of the locally manufactured generic compares very well to that of the more established Rimactazid 300 tablets, the amount of isoniazid appearing in solution in the first 15 minutes being greater for the local product, this then decreasing to values statistically equivalent to the foreign product. With respect to rifampicin, the local product appears to be statistically less soluble than either the Rimactazid 300 tabs or the Rimactane 300 caps at all times. These latter two products show a similar solubility at 15 minutes but the Rimactazid is subsequently more soluble than the Rimactane 300. Nevertheless, in vitro dissolution testing does not offer any basis for substitution of in vitro for in vivo bioequivalence testing.

Conclusion

The results achieved with chemotherapy during the last four decades should not encourage complacency. Compliance with chemotherapy depends mainly on the competence and conscientiousness of the health care team. It can be absolute if the treatment is fully and carefully explained at the very start to the patient and his family. The use of antituberculous drugs, single or combined, of demonstrated bioavailability and quality control, is recommended.

References

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