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Estimation of content of anti-TB drugs supplied at centres of the Revised National TB Control Programme in Tamil Nadu, India

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Abstract

OBJECTIVE To determine the content of certain antituberculosis (TB) drugs supplied at TB treatment centres of the Revised National TB Control Programme (RNTCP) in the state of Tamil Nadu, India.
METHODS Eight districts across the state were selected, and the following drugs were collected from five settings (District TB centre, TB unit, designated microscopy centres, DOT providers) in each district: rifampicin (150 and 450 mg), isoniazid (300 mg), pyrazinamide (500 and 750 mg), ethambutol (400 and 600 mg), ethionamide (250 mg), levofloxacin (500 mg) and cycloserine (250 mg). A maximum of 10 tablets/capsules were collected from each setting. The drugs were coded prior to analysis. All drugs were assayed by validated spectrophotometric methods. The acceptable limits for drug content were taken as 90–110% of the stated content.
RESULTS More than 90% of tablets of rifampicin 450 mg, isoniazid 300 mg, pyrazinamide 500 and 750 mg, ethambutol 400 and 600 mg and ethionamide 250 mg were within acceptable limits. Eighty per cent of rifampicin 150 mg, 21% of cycloserine 250 mg and 87% of levofloxacin 500 mg were within acceptable limits. The mean cycloserine content was below the acceptable limit in all districts, the mean drug content being 200 mg (range: 108–245 mg).
CONCLUSION This systematic study showed that the stated drug content of cycloserine was not reached in all districts. Deterioration of cycloserine could be minimised by storing the drug in refrigerators. The geographical location of the districts had no influence on the drug content.

keywords anti-TB drugs, drug content, Revised National TB Control Programme

Introduction

Tuberculosis (TB) can be effectively treated using standard short-course chemotherapy containing isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB) for drug-susceptible strains of TB Mitchison 1993. The Revised National TB Control Programme (RNTCP) in India provides quality-assured anti-TB drugs through personalised boxes. A substantial number of RMP and INH medications from several countries, especially fixed-dose combinations, were substandard Laserson *et al.* 2001; Kelesidis *et al.* 2007; : about 12% of RMP and 9% of INH collected from the private sector in two Indian cities proved substandard Bate *et al.* 2009. Bate and others assessed the quality of RMP and INH procured from private sector pharmacies in 19 cities in Africa and Asia and found that 16.6% in Africa, 10.1% in India and 3.9% in other middle-income countries were substandard and falsified drugs Bate *et al.* 2013. A few studies have also shown good quality of anti-TB medicines Ellard 1999; Ashokraj *et al.* 2004.

The RNTCP has a drug quality assurance system in place, in which samples of anti-TB drugs are tested. Drugs are mostly collected from District TB centres (DTC). The aim of this study was to determine the content of certain anti-TB drugs supplied at different TB treatment centres of the RNTCP, such as TB units (TU), designated microscopy centres (DMC) and DOT providers in the state of Tamil Nadu, India.

Materials and methods

Eight districts spread across Tamil Nadu with varying geographical terrain, accessibility and availability of DOTS plus drugs were selected. In each district, drugs were collected from DTC, TU, two DMCs and DOT

providers. Within each selected district, the TU that was geographically closest to the DTC was selected. Within the selected TU, two DMCs, one each with highest and lowest case loads, were selected. DOT providers were selected by convenience sampling. A maximum of 10 each of the following drugs was collected from each setting:

- rifampicin (RMP) (150 and 450 mg)
- isoniazid (INH) (300 mg)
- pyrazinamide (PZA) (500 and 750 mg)
- ethambutol (EMB) (400 and 600 mg)
- ethionamide (Eth) (250 mg)
- levofloxacin (LFX) (500 mg)
- cycloserine (Cs) (250 mg)

The drugs were taken from personalised patient boxes that were in current use. Boxes belonging to patients on category I/II/IV treatment during the intensive phase were selected. Collected drugs were replaced with drugs from the State Drug Stores (SDS), Chennai. For analysis, drugs stored in the SDS, and drugs purchased and used for clinical trial patients in our Institute were also included. Drugs were stored at room temperature in all the districts and in air-conditioned rooms in the SDS. All drugs were coded and sent to the laboratory for analysis; the laboratory staff was blinded regarding the source of the drugs.

Drug analysis

Drugs were assessed for their active ingredient according to validated spectrophotometric methods Rao *et al.* 1971; Jones 1956; Gurumurthy *et al.* 1984. Pure drug powder was used to prepare calibration standards of known concentrations and processed alongside the tablet/capsules. The acceptable limits for content of the active ingredient applied to the individual drugs were taken as 90–110% World Health Organisation report 2011.

Sample size calculation and statistical evaluation

It was assumed that 95% of drugs included in this study would be within the acceptable range. Considering type I error to be 5%, relative precision to be 20% with a design effect of 2, the required sample size was 10 tablets from each setting.

Statistical analysis was performed using SPSS (version 14.0). Multiple linear regression analysis was performed to determine which of the factors influenced drug content.

Results

Table 1 summarises the content of all the drugs along with outliers in all the districts. RMP 450 mg content was below the acceptable limits in one district (76%). RMP 150 mg content was below the acceptable limits in five districts. EMB 400 mg content was below acceptable limits in one district (80%). PZA 750 mg content was below acceptable limits in two districts (70% and 82%). Of the 10 tablets analysed in one TU, the mean drug content was 226.6 mg (range: 137.4–634.7 mg); nine tablets had a mean drug content of 181.3 mg (range: 137.4–235.4 mg). The content of Cs 250 mg was below acceptable limits in all the districts; 23% of tablets from the districts were within acceptable limits. The percentage of tablets falling within the acceptable limits ranged from 0 to 40%. LFX 500 mg content was below acceptable limits in three districts.

Multiple linear regression analysis was carried out to determine which of the factors (district, company and

Table 1 Drug content (Median & IQR) and the percentage adherence to stated content in eight districts

Drug	No. of tablets	Median (mg) (IQR)	No. (%) of tablets below, within & above the acceptable range		
			Below (<90%)	Within (90–110%)	Above (>110%)
Rifampicin 450 mg	398	448.6 (433.2–461.3)	26 (7)	366 (92)	6 (2)
Rifampicin 150 mg	80	151.7 (144.3–157.4)	5 (6)	64 (80)	11 (14)
Isoniazid 300 mg	406	295.2 (288.3–303.2)	16 (4)	389 (96)	1 (0)
Ethambutol 600 mg	346	600.0 (584.5–614.2)	2 (1)	335 (97)	9 (3)
Ethambutol 400 mg	94	402.5 (392.0–415.0)	1 (1)	91 (97)	2 (2)
Pyrazinamide 750 mg	406	732.2 (719.5–747.7)	22 (5)	382 (94)	4 (1)
Pyrazinamide 500 mg	17	501.0 (494.5–506.0)	0 (0)	17 (100)	0 (0)
Cycloserine 250 mg	70	212.0 (185.8–224.0)	54 (77)	16 (23)	0 (0)
Ethionamide 250 mg	64	242.0 (239.0–244.0)	0 (0)	64 (100)	0 (0)
Levofloxacin 500 mg	67	480.0 (470.0–492.0)	9 (13)	58 (87)	0 (0)

healthcare facility level) influenced drug content. Except for Cs, drugs did not have good fit as indicated by poor R^2 value. The manufacturing source was a statistically significant variable for Cs. Compared with source A, which supplied the maximum number of Cs tablets, source B had significantly lower drug levels; drug content from both sources was below the acceptable range.

Discussion

The circulation of substandard and spurious, falsely labelled, falsified or counterfeit medicines has been acknowledged to be a serious clinical and public health problem, with sales ranging from 1% in developed countries to more than 10–30% in developing countries Caudron *et al.* 2008; Newton *et al.* 2006; International Medical Products Anti-Counterfeiting Taskforce Brochure 2008. The existence of substandard anti-TB medicines has been documented in surveys from a number of countries World Health Organisation report 2011. The majority of quality problems for anti-TB medicines were due to inadequate content of the active ingredient. It is a customary in our institute to assay the content of anti-TB and antiretroviral drugs in tablets/capsules. During this process, drugs with suboptimal content are occasionally encountered, more frequently with Cs.

In this study, we determined the content of anti-TB drugs available at the RNTCP centres in Tamil Nadu. The percentage adherence to the stated content of the drugs was calculated based on that used by WHO in its survey of the quality of anti-TB drugs in the Soviet Union World Health Organisation report 2011. We observed that percentage adherence of the mean drug content to the stated content for most drugs was within acceptable limits. However, drugs not falling within acceptable limits in certain districts were occasionally observed. Batch-to-batch variations in drug content are expected to occur occasionally, but the drop in PZA content to the extent we saw in a TU in a particular district is a matter of concern. On close scrutiny, this batch of PZA tablets was not present in any other treatment centre. Hence, this could be an isolated problem restricted to this particular batch, probably due to a manufacturing deficit.

The percentage adherence of Cs to the stated content was not satisfactory in all districts; one district had content ranging from 108 to 148 mg. This district had Cs supplied by manufacturing source B, which turned out to be a significant factor influencing Cs content in multiple linear regression analysis. Cs is a second-line anti-TB drug and an important component of the DOTS plus regimen used to treat MDR TB patients. Gross deterioration of Cs during transit and storage in the tropics has been previously reported, and this was attributed to high humidity, rather than high temperature Rao *et al.* 1968. Deterioration of Cs could be minimised by storage in tightly closed containers in air-conditioned rooms (18 °C). The Cs tablets analysed in this study were directly collected from the DOT providers' home who could afford to store the drug only at room temperature; most of them lived in thatched huts. India being a tropical country has high levels of humidity and temperature for most part of the year. This problem can be solved to some extent by storing Cs in refrigerators in the DTCs and giving no more than a week's supply to the DOT provider at a time. In fact, the label suggests storing the drug in a cool place. Supply of Cs tablets with low content to patients could have serious effects, as the deteriorated product is inactive, and the margin between adequate and inadequate dosage of Cs is small Canetti 2007. Substandard manufacturing conditions coupled with adverse storage conditions could lower Cs content drastically.

Our observation of 80% of RMP 150-mg capsules falling within the acceptable range was probably due to the narrow acceptable range (135–165 mg). Further, we observed 94% of RMP 450 mg, INH, PZA 750 mg and EMB 600 mg to be within acceptable limits; the corresponding values for Cs, Eth and LFX were 23%, 100% and 87%. Our findings are strengthened by the fact that the entire analysis was undertaken in a blinded manner; drugs from SDS and those used at our institute were randomly included. Our Institute follows a stringent procedure in the purchase of drugs, and necessary precautions are taken to purchase good-quality drugs. This is especially important in viewing Cs values, as drugs with good content were also analysed alongside the RNTCP tablets. The geographical location of the districts (coastal/hilly/inland) did not influence drug content.

In summary, this study showed that the content of most anti-TB drugs adhered to stated content in Tamil Nadu, which is quite encouraging. Low content of Cs observed in all the districts is a matter of concern. It is advised to store Cs in refrigerators in the DTCs.

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