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Effectiveness and safety of the schedules of short and long term treatment for tuberculous meningoencephalitis at two hospitals of Lima - Peru

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KEYWORDS
Tuberculous meningoencephalitis;
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Abstract
Introduction: To compare the effectiveness and safety of short-term 6 month-treatment and long term 12 month-treatment schedules for meningoencephalitis due to tuberculosis in two hospitals from Lima-Peru.
Methods: Comparative, retrospective and observational study. The patients were divided in two groups: Group 1: long term 12 month-treatment with isoniazid, rifampin, pyrazinamide, and ethambutol for the first 2 months; then isoniazid and rifampin for 10 months. Group 2: short-term 6 month-treatment with isoniazid and rifampin, pyrazinamide and ethambutol for the first 2 months; then isoniazid and rifampin for 4 months. Clinical records, effectiveness, treatment failure, treatment side effects, mortality and late consequences after treatment were reviewed.
Results: Twenty-six patients with meningoencephalitis level I were included, 10 received the long term schedule and 16 the short-term schedule treatment. From 51 patients with meningoencephalitis level II, 27 received the long term schedule and 24 the short-term schedule treatment and of 31 patients with meningoencephalitis level III, 18 received the long term schedule treatment and 13 the short-term schedule treatment. There was no statistically significant differences among levels I, II and III when effectiveness of short and long term schedule was evaluated. Moreover, there was no statistically significant difference in the frequency of treatment failure, treatment side effects, mortality and late consequences among groups.

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Conclusions: Long term 12 month-treatment and short-term 6 month-treatment had similar effectiveness and safety in the treatment of meningoenchephalitis due to tuberculosis in HIV negative patients.bility in work protocols and rationalises the use of the available health care resources.

PALABRAS CLAVE
Meningoencefalitis tuberculosa;
Esquemas de tratamiento corto y largo

Efectividad y seguridad de los esquemas de tratamiento corto y largo para meningoencefalitis tuberculosa en dos hospitales de Lima-Perú

Resumen
Introducción: Comparar la efectividad y seguridad de los esquemas corto de 6 meses y largo de 12 meses en el tratamiento de la meningoencefalitis tuberculosa de pacientes VIH negativos de dos hospitales de Lima-Perú.
Métodos: Estudio comparativo, retrospectivo y observacional. Los pacientes recibieron uno de los siguientes esquemas de tratamiento: grupo 1, curso largo de 12 meses de tratamiento con isoniazida, rifampicina, pirazinamida y etambutol los primeros 2 meses; luego isoniazida y rifampicina durante 10 meses. Grupo 2, curso corto de 6 meses con isoniazida, rifampicina, pirazinamida y etambutol los primeros 2 meses; luego isoniazida y rifampicina durante 4 meses. Se revisó las historias clínicas y se evaluó en ambos grupos la efectividad, recaídas, fracaso terapéutico, reacciones adversas a fármacos antituberculosos, mortalidad y secuelas luego de concluir tratamiento.
Resultados: Se presentaron 26 pacientes con meningoencefalitis grado I, de los cuales 10 recibieron el esquema de tratamiento largo y 16 el esquema corto; 51 con meningoencefalitis grado II, 27 recibieron el esquema largo y 24 el esquema corto; y 31 con meningoencefalitis grado III, recibiendo 18 el esquema largo y 13 el esquema corto. Al evaluarse la efectividad de los esquemas corto y largo no se encontró diferencia estadísticamente significativa en los grados I, II y III; tampoco existió diferencia estadísticamente significativa en la frecuencia de recaídas, fracaso terapéutico, reacciones adversas a fármacos antituberculosos, en la mortalidad y secuelas.
Conclusiones: Los esquemas largo de 12 meses y corto de 6 meses tendrían similar efectividad y seguridad en el tratamiento de la meningoencefalitis tuberculosa de pacientes VIH negativos

Introduction

Tuberculosis (TB) is a serious world-wide public health problem. It is estimated there were 9.27 million new cases (139/100,000 inhabitants) in 2007 and that 1.7 million people died when we include co-infection with HIV cases (456,000).[1]

Tuberculous meningoencephalitis constitutes the most serious type of extrapulmonary TB. It presents itself clinically during a period of 2-8 weeks with non-specific symptoms (general malaise, loss of appetite, fever, myalgias, weight loss), followed by headache, meningism, nausea, vomiting, seizures, sensory and oculomotor dysfunction, hemiparesis, etc.[2-4] It is rated in three levels according to the *British Medical Research Council* modified severity scale:[3,5]

- Level I: alert and oriented with no focal neurological deficit.
- Level II: Glasgow scale 14-10, with or without focal neurological deficit; Glasgow scale 15 with focal neurological deficit.
- Level III: Glasgow scale less than 10, with or without focal neurological deficit.

Mortality is variable, being less than 10%, 20%-30% and 60%-70% in the levels I, II and III respectively.[3,5] The most important factor in preventing sequelae and mortality is to start treatment early.[2,3] The prognosis includes complete recovery or minimal neurological sequelae in stage I and severe neurological sequelae in stage III. The main neurological ones described are cognitive dysfunction, oculomotor alterations, hemiplegia, dysphasia, seizures, ataxia and visual impairment with optic atrophy.[4]

International recommendations state that pulmonary TB treatment for the first two months should be with 4 drugs: isoniazid, rifampicin, pyrazinamide and streptomycin, ethambutol or ethionamide.[2,6-12] There is little current evidence on extrapulmonary TB treatment, especially neurological treatment, which is recommended for 9-12 months. Although treatment with 4 drugs is accepted, there are authorities that accept 3 in areas where there is no resistance to isoniazid. There are some studies and systematic

reviews showing that (despite there being no studies comparing 6-month treatments with longer-term ones for tuberculous meningoencephalitis) short-term schedules could be enough as long as the strains of *Mycobacterium tuberculosis* are susceptible to the drugs administered.[13,14]

In Peru, according to national treatment guidelines for extrapulmonary diseases such as meningoencephalitis, treatments are undertaken on schedule I,[15] which includes 4 drugs: rifampicin, isoniazid, pyrazinamide and ethambutol. However, we have seen differences in treatment duration, as in some hospitals it is short term (6 months) and in others long term (9-12 months). Treatment duration prescribed for meningoencephalitis is based on the preferences and/or experience of the specialists.

According to the aforementioned, there is no consensus on how long treatment for tuberculous meningoencephalitis should be. Because of this, our study aim was comparing the effectiveness of long-term 12-month schedules with short-term 6-month ones for tuberculous meningoencephalitis treatment in two hospitals in Lima-Peru.

Material and methods

This was a comparative, retrospective and observational study. It included those over the age of 15 years old, of any gender, who had tuberculous meningoencephalitis confirmed by compatible symptoms and laboratory findings diagnosed by the Hospital Nacional Dos de Mayo and the National Institute for Neurological Sciences Óscar Trelles Montes (Lima-Peru) during the period 2000-2003.

Patients excluded were those with HIV infection, with other types of TB with the central nervous system as an initial form of presentation (granuloma, vasculitis, brain abscess, Pott's disease), TB affecting other organs apart from the central nervous system, decompensated disease (heart failure, kidney failure, liver cirrhosis, etc.), previous treatment, treatment abandoned for a non-medical reason and incomplete or absent clinical history.

The patients classified according to staging (levels I, II and III) received one of the following treatments:

1) *Long-term schedule:* medical recommendation of 12-month treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for the first 2 months; then isoniazid, rifampicin during 10 months.
2) *Short-term schedule:* medical recommendation of 6-month treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for the first 2 months; then isoniazid, rifampicin during 4 months.

The clinical histories of patients were reviewed by study groups. The effectiveness and safety of long-term and short-term anti-tuberculosis schedules were then assessed, together with clinical and epidemiological variables, laboratory tests, adverse reactions to anti-tuberculosis drugs (AR-ATD), relapse, treatment failure and mortality. A home visit was carried out after the total treatment had been finished at least two years previously, to analyse the sequelae. Corticosteroid treatment was also documented for both groups studied. The data was recorded in a data collection instrument.

Univariate statistics based on obtaining frequencies, percentages, measures of central tendency and relative dispersion were carried out; bivariate analysis was performed using Fisher's exact test and Student t-test for independent samples. The effectiveness and safety analyses for the anti-tuberculosis treatment schedules were performed using a multinomial logistic regression model adjusted for potentially confounding variables such as age, gender, staging, alcoholism, drug addiction and corticosteroid treatment. The calculation was performed with a 95% confidence level.

Measuring the effectiveness of a procedure attempts to ascertain the result it attains in normal conditions of use where ideal conditions are not guaranteed.[16] Our study aimed to assess the effectiveness of two anti-tuberculosis treatment schedules being administered in two hospitals in Lima-Peru, using the frequency of healed patients, failures and relapses as a parameter for effectiveness. Safety was assessed according to AR-ATD frequency. The following operational definitions were applied for the purposes of this study:

1) *Cure*: absence of clinical manifestations of tuberculous meningoencephalitis once the anti-tuberculosis treatment had finished and after 2 years of follow-up.
2) *Failure*: unfavourable clinical evolution with the need to change anti-tuberculosis treatment due to suspected resistance to the drugs.
3) *Relapse*: new episode of tuberculous meningitis in the 2 years after finishing the anti-tuberculosis treatment.
4) *AR-ATD*: non-deliberate harmful response to any anti-tuberculosis drug produced when using a normal dose for humans.

The study was approved by the Ethics Committee for Biomedical Investigation of the Hospital Nacional Dos de Mayo, which is registered at the Office for Human Research Protection (Washington DC, USA). Confidentiality of the information collected was guaranteed and was used only for the study.

Results

We recorded 145 cases of tuberculous meningoencephalitis, which were found among 205 clinical histories in the Tuberculosis Control Programme archives at the Hospital Nacional Dos de Mayo (HNDM) and the National Institute of Neurological Sciences Óscar Trelles Montes (INCN, the Spanish acronym). From these histories, 37 were excluded for being incomplete for accurate diagnosis of tuberculous meningoencephalitis. This left 108 available for analysis; 24.1% corresponded to level I (26 patients); 47.2% to level II (51 patients) and 28.7% to level III (31 patients). The disease was predominant in adolescent males and young adult males (tables 1 and 2).

Tuberculous meningoencephalitis level I

General characteristics

Twenty-six patients were included, 10 of which had received treatment on the long-term schedule and 16 on the short-term one. The general characteristics and the cytochemical analyses of cerebrospinal fluid (CSF) were similar in both groups, with the only statistically-significant difference being the gender of the patients (table 3).

Comparison of anti-tuberculosis schedules

Patients receiving short-term treatment progressed favourably, with 93.7% achieving a cure, although this

Table 1 Distribution by age of patients with tuberculous meningoencephalitis at INCN and HNDM

Agegroup	INCN	HNDM	Total	%
15-19 years	8	10	18	16.7
20-29 years	20	16	36	33.3
30-39 years	7	9	16	14.8
40-49 years	6	6	12	11.1
50-59 years	4	6	10	9.3
60-69 years	8	5	13	12.0
70-79 years	2	1	3	2.8
Total	55	53	108	100.0

percentage was 100% in long-term treatment. The mortality rate for groups that received short-term and long-term anti-tuberculosis treatment was similar, with 1 death (6.3%) in the short-term schedule group caused by liver failure and none in the long-term schedule (table 4). There was a failure rate of 6.3% in those treated on the short-term schedule and 10% in those on the long-term; there was no relapse in either of the two schedules. The AR-ATD presented in both groups also did not show significant differences, with the main ones being gastrointestinal table 5.

To analyse the presence of sequelae and disability, we carried out a home visit for 5 patients assigned to the short-term schedule and 5 on the long-term one. There were sequelae in 2/5 patients on the short-term schedule and none in those on the long-term (table 6).

Tuberculous meningoencephalitis level II

General characteristics

Fifty-one patients were included, 27 of which had received long-term schedule treatment and 24 the short-term one. The general characteristics and those of the cytochemical analysis of cerebrospinal fluid (CSF) were similar in both groups (tables 2 and 3).

Table 2 General characteristics of the groups that received anti-tuberculosis treatment for tuberculous meningoencephalitis with short-term and long-term schedules

General characteristics	Short-term schedule	Long-term schedule	Value *P**
Level I			
Number of patients	16	10	
Age	29.8±12.3 years	25.5±12.1 years	0.390
Gender			
Male	14	4	0.017
Female	2	6	
History of TB	1	0	0.615
Contact with TB	3	3	0.420
Alcoholism	2	1	0.677
Drug addiction	1	0	0.615
Diabetes mellitus	0	0	-------
Level II			
Number of patients	24	27	
Age	39.9±19.2 years	34.8±16.1 years	0.303
Gender:			
Male	13	18	0.390
Female	10	10	
History of TB	0	0	-------
Contact with TB	3	7	0.263
Alcoholism	5	2	0.122
Drug addiction	2	0	0.189
Diabetes mellitus	2	0	0.198
Level III			
Number of patients	13	18	
Age	34.5±13.5 years	42.0±22.1 years	0.248
Gender:			
Male	12	12	0.104
Female	1	6	
Previous TB	2	2	0.566
Contact with TB	3	4	0.642
Alcoholism	3	2	0.341
Drug addiction	1	0	0.419
Diabetes mellitus	0	0	-------

*Non-adjusted analysis.

Table 3 Characteristics of the cerebrospinal fluid (CSF) in patients of both groups

CSF	Short-term schedule	Long-term schedule	Value of P*
Level I			
Cells	224.2±212.3);	232.1±330.7);	0.949
Glucose	30.2±15.2mg/dl	37.9±16.3mg/dl	0.258
Proteins	121.2±68.1mg/dl	105.6±139.2mg/dl	0.747
ADA	6.6±4.6 U/l	5.6±3.5 U/l	0.572
Level II			
Cells	96.2±64.1);	137.2±132.7);	0.176
Glucose	28.6±15.3mg/dl	29.0±14.0mg/dl	0.915
Proteins	149.0±109.0mg/dl	104.2±93.5mg/dl	0.125
ADA	9.7±6.2 U/l	6.3±3.8 U/l	0.029
Level III			
Cells	80.7±58.1);	172.4±210.0);	0.112
Glucose	27.1±14.0mg/dl	27.8±15.2mg/dl	0.894
Proteins	101.9±51.3mg/dl	132.0±146.6mg/dl	0.453
ADA	7.8±4.5 U/l	8.3±5.3 U/l	0.790

* Non-adjusted analysis.

Comparison of anti-tuberculosis schedules

The mortality rate for the groups that received short-term and long-term anti-tuberculosis treatments was similar, with 5 deaths (21.7%) in the short-term schedule and 6 (21.4%) in the long-term one; the rest of the patients progressed to a cure. There was a failure rate of 12.9% in those with the short-term treatment and 5% in those with the long-term; the only relapse occurred in a patient on the short-term schedule. The main causes of mortality in both groups were superimposed infections and intracranial hypertension (table 4). The AR-ATD of both groups also did not show significant differences, with the main ones being gastrointestinal (table 5).

Table 4 Causes of mortality in patients with tuberculous meningoencephalitis who received treatment on short-term and long-term schedules

Causes of mortality	Short-term schedule	Long-term schedule
Level I		
Liver failure	1	0
Total	1	0
Level II		
Superimposed infection	4	1
Intracranial hypertension	1	4
Liver failure	0	1
Total	5	6
Level III		
Superimposed infection	7	7
Intracranial hypertension	3	5
Convulsive status	1	0
Total	11	12

To analyse the presence of sequelae or disability, we carried out a home visit on 22 patients assigned to the short-term schedule and 24 on the long-term one. There were sequelae in 14/22 patients that received short-term treatment and 14/24 that received long-term. There was not a greater frequency of sequelae (P=.473) with using short-term treatment compared to long-term.

The most commonly-found sequelae were pyramidal dysfunction (hemiparesis, asymmetric reflexes, Babinski sign and spasticity), cerebellar dysfunction (gait and limb ataxia) and changes in behaviour (less tolerance, greater

Table 5 Adverse reactions to anti-tuberculosis drugs (AR-ATD) with Table 5 Adverse reactions to anti-tuberculosis drugs (AR-ATD) with short-term and long-term schedules

AR-ATD	Short-term schedule	Long-term schedule
Level I		
Optic neuritis	0	1
Liver failure	1	0
Gastrointestinal	4	3
Total	5	4
Level II		
Liver failure	1	1
Gastrointestinal	5	10
Liver failure and gastrointestinal	0	2
Total	6	13
Level III		
Liver failure	0	2
Gastrointestinal	3	3
Total	5	4

Table 6 Frequency of side effects in groups that received treatment on short-term and long-term schedules

Side effect	Level I		Level II	
	Short-term schedule	Long-term schedule	Short-term schedule	Long-term schedule
Symptomatic psychoses	2	–	–	–
Pyramidal dysfunction	–	–	–	1
Sensorial dysfunction	–	–	1	2
Cerebellar dysfunction	–	–	2	4
Oculomotor dysfunctions	–	–	1	1
Schizophrenia	–	–	1	–
Extra-pyramidal dysfunction	–	–	1	–
Cognitive deterioration	–	–	1	1
Dementia	–	–	2	2
Amaurosis	–	–	–	1
Hearing loss	–	–	–	1
Alterations in sphincter control	–	–	–	1
Change in behaviour	–	–	2	4

irritability). The last were associated to a dysfunction of which the patient was aware (pyramidal, cerebellar, sphincter control). This is shown in table 6.

There was only one relapse, in a patient treated on a short-term schedule. The patient was later cured upon receiving treatment used for previously-treated patients, but was left with dementia.

Tuberculous meningoencephalitis level III

General characteristics

Thirty-one patients were included, 13 of which had received treatment on the long-term schedule and 18 on the short-term one. The general characteristics of the patients, together with the cytochemical analysis of cerebrospinal fluid (CSF), were similar in both groups, with no statistically-significant differences being found (tables 2 and 3).

Comparison of anti-tuberculosis schedules

When the mortality of the groups that received anti-tuberculosis treatment was compared, we saw that it was slightly higher in the short-term schedule group as compared to those on the long-term schedule (84.6% vs 66.7%); the remaining patients progressed to a cure. The cause of mortality can be seen in table 4.

There were no cases of failure or relapse. The most common AR-ATD in both groups was gastrointestinal (table 5). The high mortality in this stage, together with patients' changes of address, did not allow for location, home visit and sequela analysis.

Multivariate analysis

Multivariate analysis adjusted to variables of age, gender, staging, alcoholism, drug-addiction, and corticosteroid treatment showed that there was no significant difference for cure (P=.537) and failure (P=.092) between the short-term and long-term anti-tuberculosis treatment schedules. However, the presence of a single patient with relapse made multivariate analysis unnecessary. With regards to safety, there was no significant difference between the AR-ATD for both treatments (P=.242).

Discussion

Tuberculous meningoencephalitis is a serious infection of the nervous system that mainly effects people from third-world countries. Non-specific symptoms and tardiness in diagnosis give rise to a high mortality and neurological sequelae.[2,4,17,18] The first attempts to establish a short-term schedule for treatment[19] go back to 1980; since then, there have been several studies on adults that have shown contradictory results regarding efficacy and effectiveness[13,14,20,21] and a high rate of adverse reactions such as hepatitis in short courses using isoniazid, rifampicin and pyrazinamide.[22]

This research shows that there is no significant difference in the effectiveness of anti-tuberculosis short-term schedules of 6 months and long-term ones of 12 months to treat tuberculous meningoencephalitis (table 7). The safety analysis frequently showed the presence of AR-ATD; however, there was no statistically-significant difference between both groups of research. The most common adverse effects were liver disease and gastrointestinal.

This shows that the short-term treatment schedule for tuberculous meningoencephalitis is feasible; it would lower treatment costs and optimise resources, providing effectiveness and safety similar to the long-term schedule. We must point out that these findings were seen for levels

Table 7 Summary diagram for effectiveness and safety parameter for the anti-tuberculosis treatment schedules studied

Parameters	Short-term schedule (%)	Long-term schedule (%)
Cure	66.7	68.7
Mortality	33.3	31.3
Failure	8.3	4.2
Relapse	1.6	0
AR-ATD	31.7	35.4

I, II and III of the disease, with the difference that prognosis and survival decreased according to the level of the pathology. The results of this study agree with those obtained by Alarcón (1990) and van Loenhout-Rooyackers (2001).[13,14]

There was only one relapse during the follow-up of patients with meningoencephalitis level II (there were no relapses in levels I and III) in the group treated with the short-term schedule. There was no difference comparing the relapses in both groups, a finding similar to the only meta-analysis that compared both types of treatment.[14]

In cured patients, the presence of sequelae and disabilities were similar in those treated on both schedules. The main sequelae diagnosed were change of behaviour, pyramidal dysfunction, cerebellar dysfunction, cognitive deterioration and dementia; this is consistent with statistics reported internationally for this pathology. A greater frequency of sequelae was reported in stage II, in relation to those indicated in some reports.[3]

One of the limitations of of the study is its retrospective character; however, the selection of patients according to the inclusion and exclusion criteria and the use of multivariate analysis to control confusing aspects such as age, gender, stage, alcoholism, drug addiction and treatment with corticosteroids has, in our opinion, allowed us to carry out a proper effectiveness and safety analysis. Likewise, there is a lack of clinical trials for tuberculous meningoencephalitis treatment, mainly due to ethical reasons, which is why retrospective studies represent an alternative.[23] We consider that the results of this research are reliable because the groups set out do not differ significantly in their characteristics, indicating that they are statistically comparable. On the other hand, it was also necessary to compare levels I, II and III separately due to the fact that each group has differences in sequelae and mortality.

To conclude, both the long-term 12-month schedule and the short-term 6-month schedule had similar effectiveness and safety in tuberculous meningoencephalitis treatment in HIV-negative patients.

Conflict of interest

The authors declare no conflict of interest.

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