ORIGINAL ARTICLE

AFRICAN JOURNAL OF CLINICAL AND EXPERIMENTAL MICROBIOLOGY JANUARY 2009 ISBN 1595-689X VOL 10(1)
AJCEM/2008106/20907 -http://www.ajol.info/journals/ajcem

AFR. J. CLN. EXPER. MICROBIOL. 10(1): 47- 55

COMPARATIVE COST-EFFECTIVENESS ANALYSIS OF STREPTOMYCIN AND ETHAMBUTOL IN THE TREATMENT OF TUBERCULOSIS IN A UNIVERSITY TEACHING HOSPITAL IN NIGERIA.

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ABSTRACT

Healthcare organizations, governments and individuals have been forced by prevailing circumstances of economic crisis to be increasingly oriented towards cost containment due to escalating nature of health expenditure.

***Objective*:**

The objective of this study is to determine the comparative cost effectiveness of various anti-tuberculous therapeutic options and to make recommendation for the adoption of cost-effectiveness evaluations in National Health Policy formulation and decision-making.

Method

Retrospective cost effectiveness analysis was carried out for prescribed/dispended antibiotic to outpatients with tuberculosis among other infectious diseases in outpatients case notes between 2005 and 2007 in Ahmadu Bello University Teaching Hospital, Zaria Nigeria.

Results

The result shows that ethambutol tablet cost N8.40/unit of effectiveness while streptomycin injection cost N81.50/unit of effectiveness in the treatment of tuberculosis. Ethambutol tablet therefore appears to be more cost effective than streptomycin injection. Subjecting the cost and effectiveness to sensitivity analysis did not change this conclusion. Statistical analysis shows that there is a statistically significant difference in the effectiveness (outcome) of ethambutol (95%) and streptomycin injection (76.73%) (X^2 =13.75; $p<0.5$). Therefore there is association between effectiveness and therapeutic option chosen with ethambutol tablet being a more cost effective option. The result of this study is significant because ethambutol is usually traded off for less cost-effective streptomycin in many cases even when there is no contraindication to the use of ethambutol.

CONCLUSION

Ethambutol tablet is more cost effective than streptomycin injection at their usual therapeutic doses in combination with isoniazed, rifampicin and pyrazinamide in the treatment of tuberculos[1] at the intensive phase.

KEYWORD: Pharmacoeconomics, cost effectiveness analysis, ethambutol, streptomycin, tuberculoses.

INTRODUCTION:

Orientation towards cost containment due to escalating nature of health expenditure is continuously increasing. Only few data also exist regarding the

actual cost and benefits attributed to specific drug therapy in spite of widespread use of pharmaceuticals. This is probably due to lack of well-defined methodologies to evaluate medical intervention. Health sector capital income is low, whereas this increase in expenditure does not necessarily translate into increase per head or access.(1)

The health system is clearly in a state of rapid evolution. Traditional approaches to healthcare decisions will no longer suffice, as they are not effective in curtailing cost objectively, therefore new tools need to be employed.

Cost-effectiveness analysis, a form of pharmacoeconomic tool appears more effective if applied properly in therapeutic decision making. The various outcome of therapy namely, economic, clinical and humanistic (psychosocial) outcomes are considered (1). A comparative cost-effectiveness analysis was carried out for streptomycin and ethambutol in the treatment of tuberculosis in Ahamadu Bello University Teaching Hospital, Zaria, Nigeria.

MATERIALS AND METHODS

A retrospective study involving time and motion studies in conjunction with standard cost accounting techniques was carried out.

Patients

allocation is increasing partly due to population growth and partly due to new health development. This trend is not only observed in developed economy but also in developing ones like Nigeria where per

The study addressed adult outpatients in the Outpatients Department of Ahmadu Bello University Teaching Hospital, Zaria with tuberculosis among other infectious diseases confirmed by necessary diagnostic tools. (Table 3).

Data Collection

A total of 1018 outpatient case notes for tuberculosis were consecutively examined using diagnostic cards. These are essentially diseases that have antibacterial agents as the

mainstay of therapy. One hundred and ten (110) of the patients suffered from tuberculosis.

A total of 1527 dispended prescription were sample systemically and examined. Relevant information on prescribed/dispended drugs between the year 2005 and 2007 were extracted and recorded. These included patient demographic data, diagnosis, concurrent illness, diagnostic test (if any), drug prescribed, dosage, duration of therapy, physician's remarks on each visit and cost of drugs as well as treatment outcome.

Computation of Data

The cost per Defined Daily Dosage (DDD) of each antibacterial was calculated. DDD units are recommended by World Health

Organization (WHO) for analysis of drugs use. DDD represents the usual dosage of an antibacterial per day (e.g Ampiclox 2g per day in 4 divided doses) (2).

Cost-effectiveness Analysis

Analysis of cost (in monetary units), and effectiveness in natural units (eradication of bacteria and clinical cure):

Conduction of Cost-Effusiveness Analysis (3, 4)

Definition of Pharmacoeconomic problem

Should Option I be recommended or Option II (Table 3) as therapy of choice for the treatment of tuberculosis?

Definition of the goal and objectives of problem situation

The objective is to determine which of the treatment options provide greater value for money using effectiveness rating (table 4), decision analysis (Table 3), cost of therapy (Table 6) and coast-effectiveness analysis (table 7)

Perspective

Economic perspective of the health institution was chosen since the drugs were prescribed there. However, patient perspective was considered where necessary

a. Enumeration of the different ways to achieve the objective (Table 4)
   Consideration of valuable/ preferred treatment options.
b. Determination of Costs of therapy

Only direct medical costs were included in the analysis. These include overhead and operating costs such as acquisition costs of the drugs. Staff time (costs associated with preparation, dispensing, administration of product) where it differs from the two options considered. Others include equipment, disposa and transport costs to patient. The cost per defined daily dosage (c/DDD) of each drug was used (Table 6)

Time and motion studies was carried out for Pharmacists and Nurses that differed between each option. There was no statistically significant difference between the frequency of physician visits among the two treatment options considered being outpatients. The time and motion studies involved observing the actual work of each personnel. This included the preparation and administration of injection and dispensing of tablets. Each activity was timed using a stopwatch and the average time for 10 random observations for the completion of each of the tasks was determined. The mean salary for the healthcare personnel was obtained from the accounts section of the hospital and calculated as follows:

Mean salary/sec = $\frac{\text{Annual Salary}}{\text{Hrs./wk x No. of wrks/annum x 360}}$

The individual costs were converted into cost per dosage regimen.

Discounting

No adjustment for inflation or discounting was made for the analysis. Costs were fairly stable and both options were used within each year under review. However, slight variation over the period of time required in some cases led to the use of mean cost of each option.

Consequences (Outcomes) of each treatment option.

The literature was reviewed for positive and negative outcomes of each treatment options (Table 4) (4-9)

Sensitivity Analysis

Sensitivity analysis was performed to test whether the decision changes when specific variables altered within reasonable range in favour of less cost effective option. This was carried out for the cost of treatment options and effectiveness(Table 8)

Data Analysis

Statistical analysis was carried out on the results obtained. The effectiveness rating (percentage, proportion) was compared by the use of Chi-square analysis.

RESULTS

Table 1: COST EFFECTIVENESS ANALYSIS (CEA):-

	Cost of therapy	**Effectiveness (E)**	**CEA ($^{C}/_{E}$)**
Ethambutol Tablet 400mg b.d. x $^{3}/_{12}$ (Option I)	N798.183	95	N8.40/Unit of effectiveness
Streptomycin Inj. 1gm o.d. x $^{3}/_{12}$ (Option II)	N6,253.80	76.73	N81.50/Unit effectiveness

Using Ethambutol Tablet (option I) in combination with Isoniazid, Rifamficin and pytazinamide at the phase I (intensive phase) of Tuberculosis chemotherapy as a course of 400mg bid x $^{3}/_{12}$ cost N798.12 with effectiveness measure of 95 and cost effectiveness of N8.40/unit of effectiveness while streptomycin injection as an alternative option at a course of 1gm o.d x $^{3}/_{12}$ cost N6,253.80 with effectiveness measure of 76.73 and cost effectiveness of N81.50/unit of effectiveness.

Ethambutol tablet 400mg bid x $^{3}/_{12}$ is therefore cheaper per unit of effectiveness than streptomycin injection 1gm o.d x $^{3}/_{12}$ when used in combination with Isoniazed, Rifampicin and pyrazinamide in the Phase I(Intensive phase) chemotherapy of tuberculosis.

There is statically significant difference in the effectiveness (outcome) of ethambutol (95%) and streptomycin injection (76.73%) ($X^2 = 13.75$; $p<0.05$).

Therefore there is association between effectiveness and therapeutic option chosen.

Table 2: SENSITIVITY ANALYSIS

S/NO	ALTERATION IN VARIABLE	COST EFFECTIVENESS
1	Increasing the cost of Ethambutol tablet by 300%	N33.61/Unit of effectiveness
2	Increasing the effectiveness of streptomycin to 95% (Ethambutol value)	N65.83/Unit of effectiveness
3	Decreasing the cost of streptomycin by 50%	N40.75%/Unit of effectiveness
4	Decreasing Nurse's preparation and administration time of streptomycin to 30 sec/day	N66.60%/Unit of effectiveness

Sensitivity analysis (what if analysis) indicates that the decision still remain valid as ethambutol is still more cost effective than streptomycin despite alterations made in favour of less cost effective Streptomycin.

DISCUSSION

Antimicrobial agents constitute the largest group of drug purchased in many countries and account for the highest proportion of drug budget [7,8], therefore efforts to ensure greater cost effectiveness is indispensable in view of limited resources. Studies have shown that both ethambutol and streptomycin are predominantly used to prevent emergence of resistant strain of *Mycobacterium tuberculosis*, the causative agent of tuberculosis (7, 8, 9, 10)

This justifies their inclusion in the intensive phase (Phase I) of treatment where either of them could be used based on cost and outcome of therapy (economic, clinical and humanistic) and individual patient peculiarity. The use of streptomycin injection was found to be very rampant while ethambutol table is seldom used, even when there is no contraindication to its use in the study setting in spite of being more cost effective. This result can be used as a tool to change the prescribing habit of doctors to a more rational one. This is in agreement with the objective of pharmacoeconomic study that makes a person or a group changes their behaviour and persuade them hat a new course of action is a 'better' one. 'Better' simply means in economic terms, it is more cost efficient [11]. The result of this study agrees with the report of the British National Formulary that streptomycin is no longer popular as Phase I anti-tuberculous drug in many developing countries (12). The statistically significant differences in the effectiveness of Ethambutol (95%) and Streptomycin injection (76.73%) ($X^2= 13.75$; $p<0.05$) could probably be due to differences in their economic clinical and humanistic outcomes[7].

Ethambutol tablet being an oral preparation has no risk of infection, abscess or pain at the site of injection. It therefore achieves 100% benefit of

safety of administration compared with average of 33.7% for streptomycin injection's documented risk of infection (50%), risk of abscess (50%), pain at site of injection (99%) with only 1% likely to be free from pain [5,6,10].

Table 3: Treatment Options for Cost- Effectiveness Analysis

DISEASE CONDITION	DIAGNOSTIC TOOLS	TREATMENT OPTION	
		Option I	**Option II**
Pulmonary Tuberculosis	**Matoux test, AFB, X-ray, Microscopy, culture and sensitivity (m/c/s)**	**Ethambutol tab 400mg bid $^{3}/_{12}$ in combination with Isoniazid, Rifampicin and Pyrazinamide**	**Streptomycin inj 1gm o.d x $^{3}/_{12}$ in combination with Isoniazid, Rifampicin and Pyrazinamide**

Table 4: Effectiveness Rating.

CRITERIA	TABLET ETHAMBUTOL	VALUE	STREPTOMYCIN INJ	VALUE
1.Spectrum of activity Assumption	Bacteriosatic with some reported bactericidal activity (intracellular) Both of them can achieve the desired therapeutic outcome is used effectively; 100% sensitivity assumed.	100%	Bactericidal action; intracellular lack intracellular [5,6] (action). It is effective in preventing the emergence of resistance to other anti-tuberculous drugs but add little if anything to the bactericidal and sterilizing action of Isoniazid, Rifampicin and Pyrazinamide	100%
2.Pharmacokinetics	Oral absorption 80% Pre-systemic metabolism Nil Bioavailability 80% Plasma t½ 10-15h Frequency of administration o.d	80%	Oral absorption not applicable Pre-systemic metabolism (im) Nil Bioavailability (i.m inj. 100% Plasma t½ 2.4-9.oh Frequency of administration o.d	100%
Safety of administration	Risk infection nil Risk of abscess nil Pain at site of injection nil Tolerability 100%	100%	Risk infection 50%} Risk of abscess 50%} 66.3% Pain at site of injection 99% Tolerability (100-66.3)%	33.7%
A Adverse Drug Reaction (ADR)	Dose dependent optic neuritis (easily reversible) at 15mg/kg<1% at 25mg/kg<5%. Colour blindness Allergic rashes, Jaundice reported Tolerability (100-5)%	95%	Ototoxic [5,6] progressive damage less reversible Vestibular 2.5% ditory lss common Hypersensitivity; very common 75% (can as well pharmacist and nurses for handling) Tolerability (100-50)%	50%

Table 5: Decision Analysis.

CRITERIA	TABLET ETHAMBUTOL (OPTION I)			INJ STREPTOMYCIN (Option II)		
	Value (%)	Assigned Weight	Criterion rating	Value (%)	Assigned Weight	Crit
1. Spectrum of anti tubercular activity	100	0.4	40	100	0.4	40
2 Pharmacokinetics	80	0.2	16.0	100	0.2	20
3. Safety of administration	100	0.2	20.0	33.7	0.2	6.7
4.Tolerability (100-DR)%	95	0.2	19.0	0	0.2	10
Sum Of Criteria Ratings	-	1.0	95.0	-	1.00	76.7

COST OF THERAPY

Only direct medical costs, were considered. This include drug acquisition cost, costs associated with preparation, dispensing, administration and transport cost (to patient).

TABLE 6: Duration of therapy: Three months intensive phase (phase I) treatment.

OPTION I ETHAMBUTOL TABLET	OPTION II STREPTOMYCIN INJECTION
Acquisition Cost = C/DDD x DOT in days = 400mg bid x 3/12 in days = 8.00 X 84 = N672.00 Cost of dispensing by Pharmacist = =0.2680 X 135 secs = N36.18 Transport cost by patient (three monthly trips to refill prescription) N30/trip = N30 x 3 = 90.00 Total = N798.18	Acquisition Cost =1gm o.d x 3/12 = (C/DDD x DOT) = 25.0x84 = 2,100= (N70/5gm vial, N10/needle & syr, N5/water for Inj) cost of preparation and administration by Nurses = 0.1945 x 100 sec/day x 84 days =1,633.80 Transport cost by patient (N30 per trip day) for injection a consideration) = N30 x 84 N2,520 Total N6,253.80

Table 7: Cost Effectiveness Analysis (CEA)

OPTION I ETHAMBUTOL TABLET	OPTION II STREPTOMYCIN INJECTION
Cost = N798.18, Effectiveness = 95 CEA = 798.18 / 95 = N8.40/Unit of effectiveness	Cost = 6,253.80, Effectiveness = 76.73 CEA = 6,253.80 / 78.8 = N81.50/unit of effectiveness

Table 8 :SENSITIVITY ANALYSIS

i. Increasing cost of Ethambutol tablet by 300% (N3192.72) CEA 3192.72 = N33.61 unit of effectiveness 95
i. Increasing the effectiveness of Streptomycin to 95% (Ethambutol value) CEA 6253.80 = N65.83/unit of effectiveness 95
iii. Decreasing cost of streptomycin 50% (N3126.90) CEA 3126.90 = N40.75 unit of effectiveness 76.73
iv. Decreasing Nurses' preparation and administration time of streptomycin injection to 30 sec/day instead of 100 sec/day. This increases cost of therapy with streptomycin to N5110.14. CEA 5110.14 N66.60/unit of effectiveness 76.73

Sensitivity analysis ("what if') indicates that the decision still remain valid, as Ethambutol is till more cost effective.

This humanistic outcome enhances the effectiveness rating of Ethambutol tablet over Streptomycin injection. Ethambutol has also been reported to be tolerated in 95% of patie nts on it while Streptomycin injection's tolerability is estimated to be 50%.

This explains why individual patient peculiarity must be considered in choice of therapeutic option. For example, young children whose visual acuity can hardly be monitored objectively should not be given ethambutol. Also in patient with optic neuritis. The various adverse reaction of streptomycin, such as ototoxicity, nephrotoxicity, teratogenicity and hypertensivity reactions need to be considered as well.

CONCLUSION AND RECOMMENDATIONS

It is concluded that Ethambutol tablet at a course of 400mg bid x $^{3}/_{12}$ is more cost effective than i.m streptomycin inj. 1gm o.d. x $^{3}/_{12}$, each in combination with isoniazid, rifampicin and pyrazinamide at the intensive phase (Phase I) of anti-tuberculous therapy.

A very functional anti-tuberculous drug policy and evidence based treatment guidelines should be put in place if anti-tuberculous drugs are to be used in a cost-effective manner.

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