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Comparative pharmacoeconomic analysis of benzathine penicillin and procaine penicillin in the treatment of early syphilis in a University Teaching Hospital in Nigeria

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Abstract

Comparative pharmacoeconomic analysis of benzathine and procaine penicillin in the treatment of early syphilis in Ahmadu Bello University Teaching Hospital, Zaria, northern Nigeria was carried out retrospectively for prescribed/dispensed antibacterial drugs to outpatients with early syphilis among other infectious diseases, by examining outpatients case notes between 2005 and 2007. Results show that benzathine penicillin cost ₦ 4.31/unit of effectiveness while procaine penicillin injection cost ₦ 18.19/unit of effectiveness in the treatment of early syphilis. Benzathine penicillin injection therefore appears to be more cost effective than procaine penicllin 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 benzathine penicillin and procaine penicillin injection, (56.2%) (χ^2 = 48.58, P<0.5), Therefore there is association between effectiveness and therapeutic option chosen with benzathine penicillin being a more cost effective option. The result of this study is significant because benzathine penicillin is usually traded off for less cost-effective procaine penicillin in many cases even when there is no contraindication to the use of benzathine penicillin. Benzathine penicillin injection is more cost effective than procaine penicillin injection at their usual therapeutic dose in the treatment of early syphilis.

Keywords: Pharmacoeconomics; Cost effectiveness analysis; Benzathine penicillin; Procaine penicillin, Syphilis

Introduction

Orientation towards cost containment due to escalating nature of health expenditure is continuously increasing. Only few data 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 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 capital income is low, whereas this increase in expenditure does not necessarily translate into increase per head or access (Kozmal *et al*., 1993). The health

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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 effective if applied properly in therapeutic decision making. The various outcome of therapy namely, economic, clinical and humanistic (psychosocial) outcomes are considered (Kozmal *et al*., 1993). A comparative pharmacoeconomic evaluation, using cost-effectiveness analysis was carried out for benzathine penicillin and procaine penicillin in the treatment of early syphilis in Ahmadu Bello University Teaching Hospital, Zaria, Northern Nigeria.

Experimental

A retrospective study involving time and motion studies in conjunction with standard cost accounting techniques were used.

Patients. The study addressed adult out-patients in the Outpatients Department of Ahmadu Bello University Teaching Hospital, Zaria with early syphilis among other infectious diseases confirmed by necessary diagnostic tools. (Appendix I).

Data Collection. A total of 1018 outpatients case notes for selected disease were consecutively examined using diagnostic cards. These are essentially diseases that have antibacterial agents as the mainstay of therapy. 108 of the patients suffered from early syphilis. A total of 1527 dispended prescription were sampled systematically and examined. Relevant information on prescribed/dispensed 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.

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 four divided doses (Nerthemier, 1986).

Cost-Effectiveness Analysis. Analysis of cost in monetary units and effectiveness in natural units (eradication of bacteria; a clinical cure). Conduct of Cost-Effectiveness Analysis was done by following the procedure of WHO (1994), Cano and Fujita (1998).

a. Definition of Pharmacoeconomic problem: Should Option I be recommended or Option II (Appendix I) as therapy of choice for the treatment of tuberculosis.
b. 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 (Appendix II), decision analysis (Appendix III), cost of therapy (Appendix IV) and cost -effectiveness analysis (Appendix V)
c. Perspective. Economic perspective of the health institution was chosen since the drugs were prescribed there. However, patient perspective was considered where necessary.
d. Enumeration of the different ways to achieve the objective (Appendix II) Consideration of valuable/ preferred treatment options.
e. 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, disposal, transport costs to patient, treatment etc where applicable. The cost per defined daily dosage (C/DDD) of each drug was used (Appendix IV).

Time and motion studies were carried out for Pharmacists and Nurses that differ between each option. There was no statistically significant difference between the frequencies of physician visits among the two treatment options considered in outpatients. The time and motion studies involve observing the actual work of each personnel. These include the preparation and

administration of injection and dispensing of tablets. Each activity was timed using a stopwatch and the average time 10 random observations for the completion of each of the tasks were determined. The mean salary for the healthcare personnel was obtained from the accounts section of the hospital and calculated as follows:

Mean salary/sec = Annual Salary ÷ (Hours/week x No. of weeks/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 review. However, slight variation over the period under require 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 option (Sommer, 1989; Lampitia, 1990; Brycesson, 1992)

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 (Appendix VI).

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 and Discussion

Result for Cost Effectiveness Analysis (CEA) is presented in Table 1 while that of Sensitivity analysis is presented in Table 2.

Using benzathine penicillin injection in the treatment of early syphilis at a course of 2.4million unit stat cost ₦414.45 with effectiveness measure of 96.08 and cost effectiveness of ₦4.31/unit of effectiveness while procaine penicillin injection as an alternative option at a course of 1.2 million o.d x $^{10}/_{7}$ cost ₦969.60 with effectiveness measure of 53.2 and cost effectiveness of ₦18.19/ unit of effectiveness. Benzathine penicillin injection 2.4 million unit stat is therefore cheaper per unit of effectiveness than procaine penicillin injection 1.2 million unit o.d $^{10}/_{7}$ when used in the treatment of early syphilis.

There is statistically significant difference in the effectiveness (outcome) of benzathin penicillin (96.08%) and procaine penicillin injection (53.2%) (χ^2 = 48.58, $p<0.05$). There is therefore association between effectiveness and therapeutic option chosen.

Table 1: Cost Effectiveness Analysis (CEA):-

Treatment	Cost of therapy (C)	Effectiveness (E)	CEA ($^{C}/_{E}$)
Benzathine penicillin 2.4 million unit stat (option 1)	₦ 414.45	96.08	₦ 4.31/Unit of effectiveness
Procaine penicillin injection 1.2 million unit o.d x $^{10}/_{7}$ (option II)	₦ 969.60	53.2	₦ 18.19/Unit effectiveness

Table 2: Sensitivity Analysis

S/N	ALTERATION IN VARIABLE	COST EFFECTIVENESS
1	Increasing the effectiveness of procaine penicillin to 96.08 (option 1 value)	₦10.09/Unit of effectiveness
2	Increasing the cost of Benzathine penicillin by 100%	₦8.63/Unit of effectiveness
3	Decreasing the effectiveness of option 1 to 53.2% (option II value)	₦7.79/Unit of effectiveness

APPENDIX I: Treatment option for Cost Effectiveness Analysis

Disease Condition	Diagnostic tools	Treatment options	
		Option 1	Option II
Early Syphilis	1. Demonstration of Spirochetes with a dark - field Microscope. 2. VDRL	Benzathine penicillin injection 2.4 million unit stat	Procaine penicillin injection 1.2 million unit o.d $x^{10}/_{7}$

APPENDIX II: Effectiveness rating of drugs for the treatment of syphilis

Criteria	Inj. Benzathine Penicillin	Value	Inj. Procaine penicillin	Value
1. Spectrum of activity Assumption:	It is bactericidal and very effective for penicillin sensitive infections of which syphilis is an example-caused by *Treponema palidum* Both of them can achieve 100% Clinical cure if used in their respective doses.	100%	It is bactericidal and very effective as well for treatment of syphilis	100%
2. Pharmacokinetics	Bioavailability	100%	Bioavailability	100%
	Frequency of administration: once per treatment course	100%	Frequency of administration : once daily for 10-14 days	10%
3. Safety of drug administration	Risk of infection: once pain at site of injection, Burning pain (depot):10%	90%	Risk of infection 10-14 times: 99%	1%
4. Adverse drug Reaction	Anaphylatoid reaction 5.6% Rash, fever Local pain Tolerability =100 - ADR	94.4%	Anaphylactoid reaction 90.1% (Procaine reaction in addition) rash, fever Local pain Tolerability =100-ADR	10%

APPENDIX III: DECISION TABLE

Criteria	Inj. Benzathine Penicillin (Option I)			Inj. Procaine Penicillin (Option II)		
	Value (%)	Assigned weight	Criterion rating	Value (%)	Assigned weight	Criterion rating
1. Spectrum of activity	100	0.4	40	100	0.4	40
2a. Bioavailability	100	0.1	10	100	0.1	10
2b. Frequency of administration	100	0.1	10	10	0.1	1
3. Safety of drug administration	90	0.2	18	1	0.2	0.2
4. Tolerability	94.4	0.2	18.08	10	0.2	2
Sum of criteria rating (Effectiveness measure)		1.00	96.08		1.00	53.2

APPENDIX IV: CALCULATION OF COSTS (DIRECT MEDICAL COSTS)

Direct medical costs	Inj. Benzathine penicillin	Procaine penicillin
1. Acquisition cost of drug	2.4 million unit single dose = ₦350.00 Needle/syringe = ₦10.00 Water for inj. = ₦5.00	3ml o.d 1 vial = ₦70.00 (6ml) for 2 days 5 vials for 10 days = ₦350.00 water for injection (5) = ₦25.00 needle/syringe (10) = ₦100.00
2. Cost associated with preparation and administration	Nurse: 0.1945 x 100 sec = ₦19.45	Nurse: 0.945 x 100 sec x 10 days = ₦194.50
3. Travel cost (to patient) assuming ₦30/trip	30 x 1 (1day) = ₦30.00	30 x 10 (daily injection) = ₦300.00
Total	₦414.45	₦969.50

APPENDIX V: COST EFFECTIVENESS ANALYSIS (CEA) [CEA = Cost ÷ Effectiveness]

Treatment	Cost	Effectiveness	CEA
Option I - Benzathine penicillin	₦ 414.45	96.08	₦4.31/unit of 96.08
Option II - Procaine penicillin	₦ 969.50	66.5	₦18.19/unit of 53.2

Option I is more cost-effective.

APPENDIX VI: SENSITIVITY ANALYSIS

i. Increasing the effectiveness of procaine penicillin to 96.08 (Option I value)	Cost ÷ Effectiveness = 969.50 / 96.08 = ₦ 10.09/unit of 96.08 (Option II still less cost effective than Option I)
ii. Increasing cost of benzathine penicillin by 100%	Cost ÷ Effectiveness = 828.9 / 96.08 = ₦ 8.63/unit of 96.08
iii. Decreasing the effectiveness of Option 1 to 53.2% (option II value),	Cost ÷ Effectiveness = 414.45 / 53.2 = ₦ 7.79/unit of 53.2

Sensitivity analysis (what 'if' analysis) indicates that the decision still remains valid as benzathine penicillin is still more cost-effective.

Sensitivity analysis (what 'if' analysis) indicates that the decision still remains valid as benzathine penicillin is still more cost effective than procaine penicillin despite alterations made in favour of less cost effective procaine penicillin.

Antimicrobial agents constitute the largest group of drug purchase in many countries and account for the highest proportion of drug budget (Davey *et al*., 1992). Therefore efforts to ensure greater cost effectiveness are indispensable in view of limited resources. The result of this study is in consonance with the outcome of a study which reported that no currently recommended single dose alternatives to benzathine penicillin are available for treatment of incubating syphilis (Louis, 1999). The outcome of this study is also in agreement with announcement by the Centre for Disease Control and Prevention that, currently, intramuscular injection of benzathine penicillin is recommended for syphilis treatment, including preventive therapy for those exposed to infectious syphilis (Guideline for treatment of sexually transmitted diseases, 1998). Single-dose alternatives to benzathine penicillin could help control syphilis; none are currently available (Guideline for treatment of sexually transmitted diseases, 1998). Ten days of treatment with procaine penicillin is suggested; however, this regimen may be less effective than benzathine penicillin, particularly in non-compliant persons (Guideline for treatment of sexually transmitted disease, 1998). The result of this study is also consistent with outcome of campaign to eliminate transmission of syphilis in the United States where currently recommended dose of benzathine penicillin (2.4 million unit stat) were efficacious for syphilis prevention (Hook, 1998; Louis, 1998) as found in this study.

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 group of people change their behaviour and persuade them that a course of action is a 'better' one. 'Better simply means that in economic terms, it is more efficient (Malek, 1997). The statistically significant differences in the effectiveness of benzathine penicillin (96.08%) and procaine penicillin injection (53.2%) (χ^2 = 48.58; $p<0.05$) could probably be due to differences in their economic, clinical and humanistic outcomes (Brycesson, 1992).

Benzathine penicillin injection achieves 100% benefit of frequency of administration being once per treatment course compared with 10% for procaine penicillin given once daily for ten days.

Benzathine penicillin being given once achieves 90% benefit of safety of administration since risk of infection and pain at site of injection is once, whereas procaine penicillin, taken once daily, but for 10-14 days has only 1% benefit of safety of administration (Sommers, 1989; Lampitia, 1990; Brycesson, 1992). This humanistic outcome enhances the effectiveness rating of benzathine penicillin over procaine penicillin injection.

Benzathine penicillin has also been reported to be tolerated in 94.5% of patients on it while procaine penicillin injection's tolerability is estimated to be only 10% as a result of rampant anaphylactic reaction associated with its administration (Sommers, 1989; Lampitia, 1990; Brycesson, 1992).

Conclusion

It is concluded that benzathine penicillin injection at a course of 2.4 million unit stat is more cost effective than procaine penicillin 1.2 million unit o.d x $^{10}/_{7}$ in the treatment of early syphilis. A very functional drug formulary and comparative pharmacoeconomic analysis based treatment guidelines should be put in place if antimicrobial drugs are to be used in a cost effective manner.

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