Correspondence

Postnatal phenobarbitone for preventing hyperbilirubinaemia in newborns with ABO incompatibility

Phenobarbitone acts as an inducer of hepatic enzymes resulting in accelerated uptake, conjugation and excretion of bilirubin. Its prophylactic use in a high risk setting such as ABO incompatibility may help in reducing the need for phototherapy and exchange transfusions.

From May to December 1998, a prospective study was done at the Neonatal Intensive Care Unit, St John’s Medical College and Hospital, Bangalore. All babies with a birth weight >2000 g and gestation >35 weeks were included in the study. Babies with Rh incompatibility and perinatal asphyxia were excluded from the study. The blood group of babies born to ‘O’ group mothers was determined and those with either ‘A’ or ‘B’ blood group were included in the study. Consent was obtained from the parents and the babies were randomized to either the treatment or the control group.

The treatment group received oral phenobarbitone within 24 hours of birth in a dose of 3 mg/kg/day for the first 5 days. All the babies were assessed clinically for jaundice at 12-hourly intervals and the serum bilirubin levels were done at 24, 72 and 120 hours. Additional serum bilirubin measurements were done if the clinical examination was suggestive of hyperbilirubinaemia. Babies received phototherapy if the bilirubin level was >15 mg/dl in the first 72 hours or >17 mg/dl after 72 hours. An exchange transfusion was done only if the bilirubin levels were persistently >20 mg/dl.

The duration of hyperbilirubinaemia (bilirubin >15 mg/dl) and phototherapy given were recorded. Weights of the babies were recorded at birth and on day 3 to monitor for excess weight loss. Activity, sedation and other side-effects were also monitored in these babies. The Chi-square test was used for data analysis. The treatment and control groups were compared (50 babies each; Table I). The two groups were similar with regard to gestation, weight and serum bilirubin level at 24 hours after birth. None of the babies required resuscitation at birth and all were exclusively breast-fed. Fourteen babies (28%) in the phenobarbitone group and 26 (52%) in the control group required phototherapy (Table II). This difference was statistically significant (p=0.01).

The duration of hyperbilirubinaemia and phototherapy was about 24 hours less in the phenobarbitone group as compared to the control group (Table II). The use of phenobarbitone for the prevention of hyperbilirubinaemia was associated with a favourable outcome in the treatment group as compared to babies in the control group.

None of the babies appeared to be sedated or had decreased activity with the dose of phenobarbitone used, and the weight loss on day 3 was comparable in the two groups.

ABO incompatibility is a non-preventable cause of jaundice and almost 30%-50% of affected babies require therapy for hyperbilirubinaemia. It is difficult to predict the occurrence of hyperbilirubinaemia in babies with ABO incompatibility and a direct Coombs’ test (DCT) is an unreliable predictor of incompatibility in this setting. Hence, all babies with ABO incompatibility were included in the study. The use of phenobarbitone was effective in reducing the need and duration of phototherapy in these babies.

The results of this study are in agreement with prior studies which have used phenobarbitone as a therapeutic agent in high-risk groups such as those with Rh incompatibility and prematurity.

Phenobarbitone was effective in reducing the need for phototherapy (52%-28%). To achieve this beneficial effect, 24 babies (48%) received the drug without actually needing it. Unnecessary treatment of patients is an inherent problem with prophylactic therapy. The side-effects of any prophylactic drug should be considered prior to clinical use. No side-effects were noted with the use of phenobarbitone in the treatment group. Long term follow up studies of 5-7 years have established the safety of its short term use in the perinatal period. Nevertheless, these babies will be followed up for any long term sequelae.

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Short stay at high altitude: Risk factor for thrombosis

I read with interest the article on ‘Thrombosis as a complication of extended stay at high altitude’. I would like to comment from our experience in Nepal where thousands of sojourners and their porters trek or climb in the Himalayas during the spring and fall seasons every year. Thrombosis is seen not only with extended stay (as reported in the article) but also following a much shorter exposure (from the money saved from avoidable pharmacotherapy).

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What is pharmacoeconomics?

Pharmacotherapy is an important part of any health delivery system which has a triad of persona involved—the doctor, the patient and the third party (purchaser of a drug). Depending on the type of health delivery system the third party may in fact be the patient, the government or the insurance company. Worldwide, purchasers of health care are engaged in exercises to contain drug costs. The main impetus for these exercises is the limited availability of resources. However, as each choice made is associated with a cost, the exercise of cost containment needs to be done without impairing the quality of medical care (short term) and damaging the development of useful new drugs (long term)—an expensive and long process.

Pharmacoeconomics is a subdivision of health economics and focuses not only on the cost of drug treatment but on all issues related to the costs and benefits of the use of drugs. The availability of reliable data is paramount to the successful analysis of such issues. However, generating such data during the development of a drug and in actual-use conditions is difficult. The pharmacoeconomist’s objective in evaluating drug therapies is to assess a group of patients with a particular disorder and the use of different drugs to treat them. This includes the cost of various treatment options, costs associated with their use (additional costs of drugs/procedures in the case of adverse/toxic effects occurring), their impact on the health status (survival and quality of life), as well as other health care costs (e.g. admission to hospital, use of other drugs/procedures).

The opportunity cost of pharmacotherapy is not its actual cost but the cost or benefit which could not be undertaken elsewhere as a result of incurring the expenditure on or obtaining the benefit due to drug treatment somewhere. If money is spent on prescribing such drug treatment it is not available for other purposes; wasteful prescribing is thus seen as an affront by those who are in serious need and who would benefit from increased resources generated from the money saved from avoidable pharmacotherapy.

Cost-effective analysis is an evaluation of health benefits measured as a single outcome common to all alternative therapies, programmes or interventions. Each intervention has a different success rate in achieving a common outcome, the benefits of which can be defined and measured in natural units and the costs are measured in monetary terms, e.g. prevention of perioperative and postoperative thromboembolism by aspirin, warfarin or heparin. The analysis includes the cost of materials, adverse effects, laboratory tests, nursing and doctor time and duration of stay in hospital (which may exceed the cost of primary treatment). The costs arising from the intervention of drug therapy relates not only to the price paid for a drug but also all other costs related to its use including time lost from work and distress produced. Thus, the cost of drug therapy is direct, indirect and intangible.

Similarly, the measurement of benefits is comprehensive and can be calculated by incorporating all the impacts upon a patient’s life arising as a consequence of drug therapy, e.g. natural units: years of life saved, strokes prevented, etc; utility units: measuring the change in a patient’s satisfaction or sense of well-being as determined by the change in quality of life (QOL); and associated economic benefits measured in actual monetary units, i.e. the economic benefits that accrue to society as a consequence of sufficient improvement in the patient’s health to facilitate her/his return to work (productivity of a person).

Quality of life after medical intervention or pharmacotherapy

Most of us are familiar with the benefit of treatment in saving or extending life, i.e. life expectancy. However, the extended life may have so low a quality and functional status that it may not be worth having at all. It is therefore useful to have a unit of measurement that combines the quality of life with its quality to allow a social decision to be made on a sounder basis than mere intuition. To meet this need, a measure called quality-adjusted life-years (QALYs) has been developed where estimations of years of life expectancy are modified according to estimations of QOL. The measurement of QOL has four principal dimensions: (i) freedom from lower levels of pain and distress; (ii) physical mobility, i.e. ability to walk or climb stairs, perform household activities; (iii) capacity for self care; and (iv) ability to engage in normal work and social interactions.

The approach to measure QALYs has been developed into a questionnaire to measure what the subject perceives as personal health. These are being refined to provide an improved assessment of the benefits and risks of drugs to the individual and society.

Cost-utility analysis is similar to a cost-effective analysis with the difference that the outcome does not have to be measured on a common natural scale. It is measured in terms of the changes in patient well-being or QOL (utility). Since such an outcome is not disease-specific, analysis of the therapy compares the ‘value’ of interventions in more than one area of health care, e.g. kidney transplant with the use of erythropoietin in treating anaemia of chronic renal failure.

Cost–benefit analysis is also similar to a cost-effective analysis but has subtle differences. Both aim to determine the cost–outcome ratio (as an average or incremental) to compare alternative therapies. However, in a cost–benefit analysis, those alternatives are measured which achieve different outcomes. For example, one therapy prolongs life and improves QOL (coronary artery bypass grafting), whereas the other only improves QOL (hip joint replacement). To compare different outcomes (some positive and some negative, such as adverse effects, toxicity or adverse drug reactions), a common denominator is needed which is stable, plausible, consistent and incorporates most, if not all, outcomes. The common denominator for conversion is money. The positive and negative consequences of the medical intervention are expressed in monetary terms and aggregated to arrive at comparable cost–benefit ratios.
In a cost-minimization analysis the major outcome of interest is the same and is achieved equally by alternative regimens. This allows evaluators to concentrate on the cost side of the equation to choose an alternative with the lowest costs, e.g. whether to use a diuretic and a beta-blocker or an angiotensin-II receptor blocker to achieve a similar clinical outcome (efficacy) in a non-diabetic hypertensive patient. All other things being equal, economic efficacy requires the choosing of an option that allows the maximum number of patients to be treated within the same budget.

As a result of health care reforms worldwide, and in an attempt to improve value for money from drug therapy, the demand for pharmacoeconomic studies has increased. In order to ensure the scientific credibility of various studies and to improve clinical practice, clinicians should be acquainted with some of the principles which are used and applied in the evaluation of pharmacoeconomics.

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Prevalence of extended spectrum β-lactamase producing Klebsiella spp. causing nosocomial respiratory infections

Klebsiella spp. are an important cause of nosocomial lower respiratory tract infections (LRI). The production of extended spectrum β-lactamases (ESBL), which hydrolyse broad-spectrum cephalosporins, monobactams and anti-Gram negative penicillins, by Klebsiella spp. is a major problem in the treatment of infections caused by these bacteria. The prevalence of such strains has been reported to be 1%–58% among patients with nosocomial respiratory infections. However, there is a paucity of data on this issue from Indian hospitals.

Endotracheal secretions from patients on ventilators and with clinical evidence of LRI with or without pneumonia, admitted to the intensive care units (ICUs) of the Christian Medical College and Hospital, Vellore from March to December 2000 were cultured in a semi-quantitative manner. Klebsiella spp. isolated in moderate-to-heavy growth were tested for antimicrobial susceptibility using the National Committee for Clinical Laboratory Standards (NCCLS) recommendations. They were screened for ESBL production using cefotaxime (30 µg) and ceftazidime (30 µg) discs. Those resistant (<14 mm zone diameter) to either of the drugs were considered ESBL producers.

From a total of 590 samples cultured, 116 (19.6%) yielded Klebsiella spp. with a moderate or heavy growth. Ninety-two of these were identified up to the species level; 78 (84%) were K. pneumoniae and 7 each (8%) were K. oxytoca and K. ozaenae. Fifty-five (47%) of the 116 were resistant to both cefotaxime and ceftazidime (indicating ESBL production) and included 36 (46%) K. pneumoniae, 6 (8%) K. oxytoca and 1 (14%) K. ozaenae. Twenty-two of the 51 (43%) isolates from the medical ICU, 9/33 (27%) isolates from the neurology ICU, 8/12 (66%) isolates from the surgical ICU, 12/13 (92%) isolates from the paediatric ICU and 4/7 (57%) isolates from other units were ESBL producers. All ESBL-producing strains were susceptible to imipenem and meropenem. Only 14.5% were susceptible to gentamicin, 62% to amikacin and 44% to ciprofloxacin.

Klebsiella spp. producing ESBL account for a large proportion of hospital isolates. The absence of simple and cost-effective methods to detect ESBL-producing strains may be an important reason for their low detection in clinical specimens. The double disc diffusion and three-dimensional tests, Vitek and Etest and their modifications are either cumbersome or expensive. The recent recommendation from NCCLS is that cefotaxime 30 µg can be used to screen for ESBL production. Since the sensitivity of this test can be increased if more than one third-generation cephalosporin is used for screening, we used ceftazidime also. Although ESBL producers can be classified as intermediate or resistant by standard breakpoints, a few strains may have zone sizes above this value and hence appear sensitive. It has been recommended that isolates which yield zone sizes <27 mm for cefotaxime and <22 mm for ceftazidime should be suspected to be ESBL producers and confirmed using tests in which combinations of cephalosporins and clavulanic acid are used. However, we have only included isolates resistant to cefotaxime and ceftazidime as ESBL producers. Therefore, the actual prevalence of ESBL producing strains is likely to be higher than 47%, which is alarming. These ESBLs are mostly plasmid-mediated TEM and SHV enzymes, which can be transmitted among Enterobacteriaceae. Hence, it is important to identify these bacteria and prevent their spread in hospitals.

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