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Short communication

Effects of etoricoxib on the pharmacokinetics of phenytoin

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Abstract:
Etoricoxib is presently the most commonly prescribed cyclooxygenase-2 (Cox-2) inhibitor for chronic pain and inflammatory conditions. In clinical practice, phenytoin and etoricoxib are used in chronic conditions of generalized seizure with concomitant chronic pain. Hence, there are chances of drug-drug interaction because modulations of isoenzymes involved in metabolism CYP2C9/10 and CYP2C19 which partially inhibited by etoricoxib. It is important to maintain the therapeutic level of phenytoin in plasma for effective control of seizure. So, the aim of the study was to determine the effect of etoricoxib on the pharmacokinetics of phenytoin in rabbits. In a parallel design study, phenytoin (30 mg/kg/day) was given daily for seven days. On day 7, blood samples were taken at various time intervals between 0–24 h. In etoricoxib group, phenytoin was administered for seven days as above. On day 8, etoricoxib (5.6 mg/kg) along with phenytoin (30 mg/kg/day) was administered and blood samples were drawn as above. Plasma phenytoin levels were assayed by HPLC and pharmacokinetic parameters were calculated. In etoricoxib group, there was a decrease in $t_{½}$a phenytoin and $t_{½}$el decreased significantly as compared to phenytoin group. Significant changes were observed in the pharmacokinetic parameters in etoricoxib-treated group. These results suggest that etoricoxib alters the pharmacokinetics of phenytoin. Confirmation of these results in human studies will warrant changes in phenytoin dose or frequency when etoricoxib is co-administered with it.

Key words:
etoricoxib, phenytoin, pharmacokinetics

Abbreviations: AUC_{0-t} – area under the plasma drug concentration versus time curve, AUFS – absorption unit flow scale, C_{max} – peak plasma concentration, CYP – cytochrome P, HPLC – high performance liquid chromatography, IAEC – Institute Animal Ethics Committee, K_a – rate constant for plasma drug absorption, K_{el} – rate constant for plasma drug elimination, $t_{½}$a – absorption half life, $t_{½}$el – elimination half life, T_{max} – time to reach the peak plasma concentration

Introduction

Etoricoxib is a selective cyclooxygenase-2 inhibitor which has been marketed for treatment several arthritic conditions. It is approved for use in rheumatoid arthritis, osteoarthritis, acute gout, chronic musculoskeletal pain, postoperative pain and primary dysmenorrhea. The peak plasma concentration reached within 1 h and elimination half life is about 22 h [2, 15]. Etoricoxib undergoes hepatic metabolism mainly by CYP3A4 and also CYP2D6, CYP2C9, CYP1A2 and CYP2C19. Mostly it is a weak inhibitor of CYP3A4, CYP2D6, CYP2C9, CYP1A2, CYP2C19 and CYP2E1 [6, 10, 11, 17].

On other hand, phenytoin is one of the most commonly prescribed drugs to control generalized seizures. However, its narrow therapeutic index makes it necessary to monitor plasma levels to ensure effective

and safe therapy [7]. CYP2C19 is one of the isoenzymes involved in metabolism of phenytoin. Therefore, it is possible that during chronic therapy with phenytoin, concomitant administration of etoricoxib may lead to significant drug-drug interaction. In a developing country like India as well as in developed countries where muscular pain and arthritic condition are very common**,** there is a great likelihood of use of these analgesic compounds. Epileptic patients are usually on prolonged therapy with phenytoin, hence, these patients are likely to receive analgesics drugs. So, the purpose of the present study was to evaluate the effects of the etoricoxib on the pharmacokinetics of phenytoin in an experimental parallel design study.

Materials and Methods

Animals

Twelve randomly selected healthy male New Zealand white rabbits weighing between 1.5 kg and 2.5 kg were included in the study. The rabbits were kept under standard animal house conditions of 12/12 h day/night cycle at a temperature of 25 ± 2°C, humidity of 60 ± 2%. The animals were allowed water *ad libitum* and free access to standard food. The blood samples were drawn after application of topical lignocaine anesthesia to minimize pain to the animal. Injections were given as painlessly as possible. The study protocol was approved by the Institute Animal Ethics Committee (IAEC) of PGIMER, Chandigarh, India.

Drugs

Phenytoin and etoricoxib were used in the study. These were in bulk powder form and were dissolved in appropriate solvents prior to administration.

Study design

A parallel design study was used. Rabbits were divided into two groups, phenytoin group and phenytoin with etoricoxib group. The weights of the rabbits were between 1.5 to 2.5 kg. Animals were kept in standard laboratory conditions one week prior to the experiment to acclimatize.

Procedure

Control group (phenytoin)

Six rabbits were administered phenytoin at a dose of 30 mg/kg/day, orally at 08:00 h for seven consecutive days using an oro-gastric tube. On day 7, blood samples (1 ml) were collected before administration of the next dose of phenytoin at 0 h and then at 0, 1, 2, 3, 4, 5, 6, 7, 9, 12 and 24 h after drug administration.

Phenytoin and etoricoxib group

Six rabbits were administered phenytoin at a dose of 30 mg/kg/day orally at 08:00 h for seven consecutive days using an oro-gastric tube. After 7 days, etoricoxib (5.6 mg/kg), given orally with phenytoin (30 mg/kg /day) and blood samples were drawn at similar time intervals as mentioned above.

All blood samples were drawn from the marginal ear vein after topical anesthesia with 4% lignocaine solution. Each sample was collected in labeled, heparinized test tubes and centrifuged at 3000 rpm for 10 min. Plasma was separated by centrifugation and stored at –20°C until assayed for phenytoin by high performance liquid chromatography (HPLC) method.

HPLC method for estimation of phenytoin

Extraction procedure

To 0.2 ml of plasma sample/standard sample 0.2 ml of 1.0 M of sodium acetate buffer (pH 5.5) and 3.0 ml of chloroform were added. The tubes were shaken for 1 min and then centrifuged at 3000 rpm for 10 min. Following this, 2.8 ml of chloroform layer was transferred into another test tube and the chloroform was evaporated at 50°C in a water bath. The residue was reconstituted in 0.2 ml of mobile phase to be used for HPLC assay. 100 µl of this reconstituted solution was injected to HPLC system for assay.

HPLC conditions

The mobile phase was acetonitrile : methanol : 4 mM potassium phosphate buffer (pH 6.0) ratio of 20:40:40 (v/v/v) delivered at a flow rate of 1.0 ml/min at ambient temperature. Absorbance was measured using a UV detector at 215 nm at a sensitivity of 0.02 AUFS. The sensitivity of the assay was 0.1 µg/ml

with recovery 98% or more. Pure bulk phenytoin was used to standardized and validate the HPLC method. The standards used for phenytoin ranged from 0.5 μg/ml to 32 μg/ml [15].

Data analysis

The pharmacokinetic parameters were calculated. Peak plasma concentration (C_{max}) and time to reach the peak plasma concentration (T_{max}) were calculated from the actual plasma level data. Rate constant for plasma drug elimination i.e. K_{el} was calculated by regression analysis of the monoexponential declining line of the plasma drug concentration versus time curve, while elimination half life ($t_{½}$el) was obtained from the formula, $t_{½}el = 0.693/K_{el}$. Absorption rate constant K_a was calculated by residual method. The absorption half life ($t_{½}a$) was calculated from the formula $t_{½}a = 0.693/K_a$. Area under the plasma drug concentration versus time curve (AUC_{0-t}) was calculated by trapezoidal rule. Extension of the AUC data to infinity ($AUC_{t-\infty}$) was done by dividing the last observed concentration in plasma by the elimination rate constant (K_{el}). The $AUC_{0-\infty}$ was calculated from the sum of AUC_{0-t} and AUC $_{t-\infty}$. Statistical analysis was done using the paired Student's '*t*' test to find the level of significance. SEM was used since sample size was small (n = 6); p value ≤ 0.05 was considered statistically significant.

Results

In the control group, mean plasma levels were determined when phenytoin was given alone and the pharmacokinetic parameter calculated as described above. In etoricoxib group, mean plasma phenytoin levels were determined at different time intervals following oral etoricoxib administration. Significant changes in plasma levels of phenytoin were observed when etoricoxib was given with phenytoin compared to phenytoin controls (Fig. 1).

There was a significant decrease in the maximum plasma concentration of phenytoin (C_{max}), the time to reach maximum plasma concentration (T_{max}) was increased, the elimination half life of phenytoin ($t_{½}$el) and the area under the curve ($AUC_{0-\infty}$) were decreased when etoricoxib was given along with phenytoin as compared to phenytoin alone. There was a decrease in absorption half life with a significant decrease in elimination half life, AUC of phenytoin in the etoricoxib-treated group (Tab. 1).

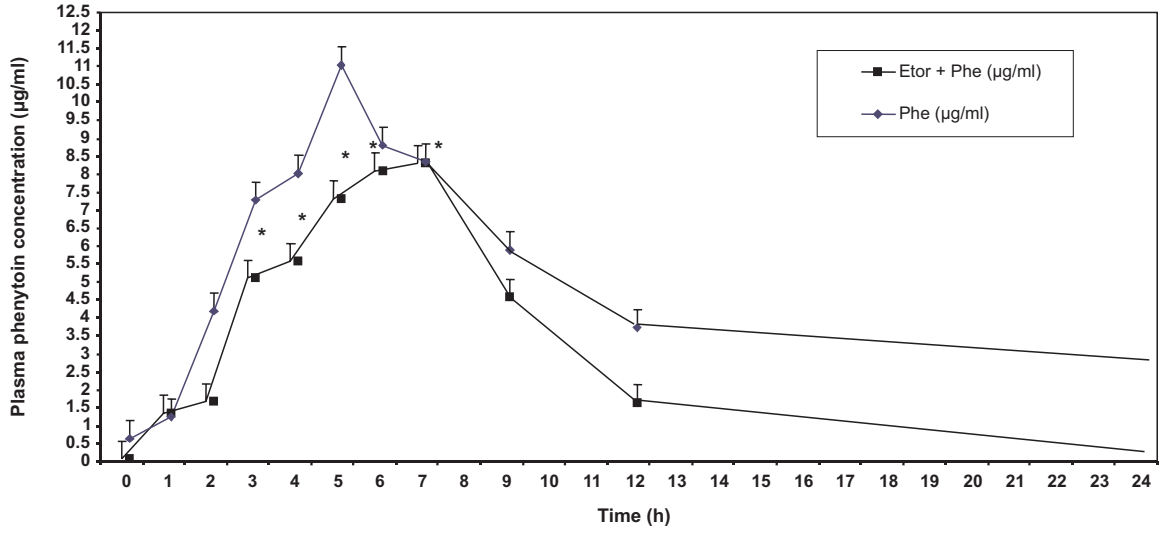

Fig. 1. Plasma phenytoin levels (the mean ± SEM) at different time intervals of phenytoin alone and following etoricoxib with phenytoin oral administration. * $p < 0.05$

Tab. 1. Different pharmacokinetic parameters of phenytoin alone and following oral administration of etoricoxib

Pharmacokinetic parameters	Phenytoin group	Phenytoin and etoricoxib group
C_{max} (μg/ml)	11.05 ± 2.12	8.3 ± 1.69*
T_{max} (h)	5.0 ± 0.88	7.0 ± 0.21*
K_a (h^{-1})	0.359 ± 0.06	0.398 ± 0.09
$t_{½}a$ (h)	1.93 ± 0.22	1.74 ± 0.09*
K_{el} (h^{-1})	0.0318 ± 0.03	0.0857 ± 0.02
$t_{½}el$ (h)	21.83 ± 0.65	8.08 ± 1.33*
$AUC_{0-\infty}$ (μg/ml/h)	60.22 ± 24.12	43.6 ± 24.21*

Values are the mean ± SEM, (n = 6); * $p < 0.05$ (Student's *t*-test was used)

Discussion

Phenytoin has a narrow therapeutic index, so it is very important to ensure that any factor likely to affect its plasma levels is taken into account and dose adjustments are made accordingly [3, 8]. Since phenytoin is given for a prolonged time, it is likely to be taken along with other drugs which may lead to an increase or decrease in its plasma levels and subsequent deleterious effects either due to toxicity or loss of effective seizure control by this antiepileptic [5].

This study attempted to evaluate any possible drug interaction that can occur if etoricoxib is concomitantly given with phenytoin. Rabbits are ideal animals for pharmacokinetic studies among smaller animals since higher animals like monkey which was commonly used in the past for pharmacokinetic study is not permitted for experiment in India. Rabbits have been used extensively in this area and show good sensitivity as well as it is more suitable for multiple sampling which is required for such studies. Drug dose calculations are based on extrapolation of human recommended doses to rabbits using conversion factor [4]. The dose used for phenytoin has been successfully used in similar experiments in our laboratory [14, 16]. The dose regimen for phenytoin was based on pilot studies which showed no significant difference in plasma concentrations of phenytoin after 7 and 14 days of administration of phenytoin in adult healthy male rabbits [13]. Dose calculation of etoricoxib was based on recommended human treatment regimes so as to closely mimic human situations of use [1].

The gastrointestinal absorption of drugs is a complex process and the rate and extent of absorption depends on several factors, like lipid solubility, formulations, splanchnic blood flow, metabolic capacity of the gastrointestinal tract and disease states [9]. Whenever two drugs are given orally there can be competition for transport processes involved in absorption. In this study, there was a 38% decrease in the elimination half life of phenytoin when etoricoxib was administered with phenytoin.

Plasma protein binding capacity of phenytoin and etoricoxib is more than 90%. Study conducted to evaluate the mechanism of interaction of etoricoxib with human serum albumin (HSA) was using fluorescence spectroscopy. There was only one class of binding site with association constants. Thermodynamic parameters suggest van der Waals and hydrogen bonding interactions in the case of etoricoxib, however, etoricoxib binds at different regions within site II. The presence of salt and pH caused significant changes in the association constants and the concentration of free pharmacologically active drug [12].

In our study also etoricoxib altered metabolism of phenytoin. These findings if confirmed in clinical studies will hold importance as even a one third increase in the half life of phenytoin will mandate some readjustment of the dosage regimen. It was seen that etoricoxib decreased the absorption half life of phenytoin significantly.

Study by Kassahun et al. [4] on metabolism of etoricoxib has shown that several isoenzymes are involved in etoricoxib metabolism CYP3A4 and also CYP2D6, CYP2C9, CYP1A2 and CYP2C19. Mostly it is a weak inhibitor of CYP3A4, CYP2D6, CYP2C9, CYP1A2, CYP2C19 and CYP2E1 [3, 17]. Therefore, this observation that etoricoxib decreases $t_{½}a$ of phenytoin needs further investigation.

Etoricoxib when given along with phenytoin decreased mean plasma levels of phenytoin. The elimination half life of phenytoin decreased by 38% of the control and there was a 71% decrease in the $AUC_{0-\infty}$, and it may be relevant in actual clinical practice where a decrease in $t_{½}el$ and $AUC_{0-\infty}$ would lead to decreased duration of therapeutic effect of phenytoin due to rapid elimination as well as decreased oral bioavailability. In such a situation, the dose of phenytoin will have to be increased to maintain adequate control of seizures. This findings suggest the in-

creased metabolism and decreased bioavailability of phenytoin when etoricoxib is given.

Current knowledge about the metabolic pathways of etoricoxib is still incomplete since it is metabolized by a complex pathway and several isoenzymes are involved. So far, only a few studies have been conducted and further elucidation of their effects on metabolic enzymes may help clarify these results in the future.

In conclusion, etoricoxib alters the pharmacokinetics of phenytoin significantly. This interaction has not been reported before. Due to ethical constraints, we have included a minimum number of animals in this study. However, the findings of this study may prove to be important in clinical settings. The results of this study need to be confirmed in drug interaction studies in humans to warrant a recommendation for altering dosage of phenytoin in patients on chronic therapy for epilepsy who require etoricoxib as a concomitant treatment for the management of chronic arthritic or inflammatory conditions.

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