Effect of nimesulide co-administration on pharmacokinetics of lithium

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Received 24 June 2004; revised 16 August 2004

In a crossover study, lithium was given orally at a dose of 56 mg/kg, prepared as suspension (0.5%) in carboxymethyl cellulose (CMC) and blood samples (1 ml) collected after 0-24 hr after drug administration. After a washout period of two weeks, nimesulide (10 mg/kg) was administered along with lithium (56 mg/kg) and blood samples were drawn at the same time intervals (0-24 hr) after drug administration. Plasma was separated and assayed for lithium by M 654 Na+/K+/Li+ analyzer and various pharmacokinetic parameters were calculated. $C_{\text{max}}$, $K_{\text{a}}$, $t_{1/2}$ and $AUC_{\text{in}}$ of lithium were significantly increased when nimesulide was administered along with lithium as compared to control group.

Keywords: Lithium, Nimesulide, Pharmacokinetics, Drug Interaction

Lithium is used for the management of hypomania/mania and depression and for prevention of recurrences of major affective illness, particularly both mania and depression in bipolar I or II disorders. Lithium is absorbed readily and almost completely from the gastrointestinal tract after oral administration reaching peak plasma levels in 2½ hr. Lithium is a drug with narrow therapeutic index and the occurrence of toxicity with lithium therapy is related to serum lithium concentration and its rate of rise following administration.

NSAIDs, prescribed widely for a variety of musculoskeletal disorders, are known to increase lithium levels in blood. This interaction is particularly serious with indomethacin. It may also occur with ibuprofen, naproxen and to a lesser extent with sulindac and aspirin.

Nimesulide, a selective COX-2 inhibitor, is widely used NSAID in India. Though, COX-2 is the inducible isoform of cyclooxygenase, it is also constitutively expressed in certain areas of kidney and brain. It can be expected, therefore, that nimesulide might interact with lithium in a manner similar to non-selective COX inhibitors as mentioned above. Recently, a case report has been published implicating lithium interaction in a patient receiving concomitant administration of nimesulide leading to lithium toxicity. Hence, the present study was designed to evaluate the pharmacokinetic interaction of nimesulide with lithium in rabbits.

Animals used—Healthy male New Zealand white rabbits (n=12) weighing between 1.5-2.5 kg and age 9-12 months were selected and kept in isolation for at least 21 days prior to experimentation. All the animals were maintained under standard laboratory conditions under 12 hr light/dark cycle at 25°C ± 2°C. The animals were fed standard pellet diet and water ad libitum.

Experimental design—An open, cross over design was adopted to study pharmacokinetic interaction between lithium and nimesulide. Rabbits, fasted overnight prior to experiment, were administered lithium orally at a dose of 56 mg/kg (extrapolated from human dose) by means of orogastric tube. Blood sample (1 ml) was collected from marginal ear vein at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hr after drug administration.

After giving a washout period of 2 weeks, rabbits were administered nimesulide (10 mg/kg, extrapolated from human dose) along with lithium (56 mg/kg). Blood samples were collected at same time intervals as mentioned above.

Estimation of lithium in blood—Blood samples (1 ml) were collected in heparinised test tubes and centrifuged at 3000 rpm for 5-7 min to separate the serum. Lithium levels were estimated by M 654 Na+/K+/Li+ analyzer (Chiron Diagnostic).

Pharmacokinetic Parameters—Peak serum concentration ($C_{\text{max}}$) and time to reach the peak serum concentration ($T_{\text{max}}$) were calculated from the actual plasma data. Absorption rate constant ($K_a$) was calculated by residual method, while absorption half-life ($t_{1/2a}$) from the formula $t_{1/2a} = 0.693/K_a$. Elimination rate constant i.e. $K_d$ was calculated by least square regression analysis, while elimination half-life ($t_{1/2e}$) was obtained using the formula $t_{1/2e} = 0.693/K_d$. Area under the serum drug concentration
versus time curve (AUC_{0-24h}) was calculated by Trapezoidal rule. Extension of AUC data to infinity was done by dividing the last observed concentration of drug in serum by elimination rate constant (K_e).

Statistical analysis—The data was subjected to statistical analysis using paired Students t test. The results were considered to be statistically significant at P<0.05.

Figure 1 shows the mean lithium levels in serum at different time intervals with and without concomitant administration of a single dose of nimesulide in rabbits. The serum lithium level increased significantly from 0.5 to 9 hr after nimesulide administration as compared to lithium alone.

Table 1 depicts various pharmacokinetic parameters of lithium alone and after single dose nimesulide. C_{max}, AUC_{0-24}, K_e, and t_{1/2}e of lithium increased significantly after single dose of nimesulide. No statistically significant difference was observed in T_{max} before and after single dose nimesulide.

The results of present study showed the presence of a pharmacokinetic drug interaction between lithium and nimesulide. It indicated that the observed increase in the bioavailability of lithium due to nimesulide was mainly due to impaired elimination of lithium by nimesulide. Lithium is known to have interaction with other drugs, like diuretics, in particular thiazides, that interfere with renal excretion of lithium. Other drugs like haloperidol, furosemide have also been reported to interact with lithium

The findings of this study were in accordance with the similar findings as those of non-selective COX inhibitors which are known to facilitate renal proximal tubular reabsorption of lithium and thereby, increase concentrations in plasma to toxic levels.

COX-2 generally is an inducible enzyme, induced by cytokines, growth factors, endotoxin, but at certain sites like kidney, it is constitutively expressed. Therefore, the probable mechanism for pharmacokinetic interaction observed in the present study may be similar to that of non-selective COX inhibitors. Nimesulide has been shown to be a selective COX-2 inhibitor in human beings at clinically recommended doses. It acts by inhibiting prostaglandin synthesis, therefore showing anti-inflammatory, analgesic and antipyretic properties. Nimesulide is widely used in India and lithium is a drug with a narrow therapeutic index, therefore, such an interaction could be clinically important. Therefore, unless proved otherwise in a clinical study, it is suggested that nimesulide to be administered with caution in patients on lithium therapy to avoid lithium toxicity.

References


