ORIGINAL ARTICLE

Intraperitoneal Administration of a Developed Targeted Brain Prodrug of Ibuprofen

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Abstract

Introduction: The efficiency of using ibuprofen for protecting the brain against Alzheimer's disease can be improved by developing a prodrug of ibuprofen able to distribute better through the blood–brain barrier (BBB). **Materials and Methods:** In this study, the hydroxyethyl ibuprofen (HEI) was synthesized as a prodrug by esterification of ibuprofen sodium through 2-bromoethanol then characterized using proton nuclear magnetic resonance and mass spectroscopy. The hydrolysis of HEI was evaluated in phosphate buffer at different pH values. Furthermore, the conversion of the prodrug to the parent drug was studied *in vitro* in rat's brain homogenates and plasma. Moreover, the kinetics of the HEI was studied in rats after intraperitoneal application in comparison to intraperitoneal injected ibuprofen. **Results:** The stability of HEI in buffer solutions decreased with increasing pH value. On the other hand, it was hydrolyzed rapidly in rat's plasma and faster than in brain homogenates. HEI was detected in plasma at low concentration for short time where it did not appear in brain. Hence, HEI is hydrolyzed in plasma to ibuprofen; the kinetic parameters of HEI were estimated by quantifying resulted ibuprofen. The bioavailability, absorption rate, and elimination rate constants of the prodrug were lower in plasma as well as in brain than of the parent drug. Furthermore, they were lower of both prodrug and parent drug in brain than in plasma. **Discussion and Conclusions:** The diffusion rate of the drug and prodrug into plasma and brain was dependent on the peritoneum membrane and BBB characteristics besides to the difference of the polarity between HEI and ibuprofen.

Key words: Alzheimer's disease, blood–brain barrier, ibuprofen, intraperitoneal, prodrug, targeted delivery

INTRODUCTION

The incidence of central nervous system (CNS) disorders is in increasing in spite of the advance in the research of their mechanisms.[1] The scientific literature revealed that nonsteroidal anti-inflammatory drugs (NSAIDs) are neuroprotective under a number of conditions including neurodegenerative diseases.[2] Many studies reported a reduced prevalence of Alzheimer's disease (AD) among treated patients by NSAIDs. However, these compounds show low blood–brain barrier (BBB) permeation that they have organic weak acids and ionized at physiological pH and also they have high protein-binding ability.[3]

To use NSAIDs efficiently against AD, adequate concentrations of these drugs must penetrate into the CNS.[4] Hence, it would require the administration large doses to reach to effective concentration in the CNS which elevate the risks of side effects. Therefore, the usage of NSAIDs is limited in the long-term drug treatment.[5]

The efficiency of CNS therapy using NSAIDs might be improved by the development of brain-targeted agents that distribute that better through BBB.[6,7] This can be achieved through prodrug approach. Prodrugs are precursors of parent drugs and *in vivo* converted to active agents by enzymatic and/or biochemical process.[3]

The most frequently used NSAIDs were diclofenac (43.2%) and ibuprofen (21.6%).[8] Furthermore, the ibuprofen and diclofenac showed the most protective effect for the AD.[9]

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The prodrugs may behave differently under *in vitro* and *in vivo* that many physiological factors *in vivo* are not present under *in vitro* conditions. Rats were selected frequently as an animal model to study the release pattern of prodrugs as there are some physiological similarities of rats with humans.[10] Intraperitoneal (ip) route is useful to inject large volumes of fluid safely also for small species for which intravenous access needs special skills. However, absorption of material delivered ip is typically much slower than for intravenous injection.[11]

This present study aimed to develop a new prodrug of ibuprofen in attempt to improve its ibuprofen through the BBB to the brain.

Experiments

Chemicals

Ibuprofen was obtained from BASF (Germany). Sodium hydroxide and sodium dihydrogen phosphate were purchased from Riedel-de Haën (Germany). Water, acetonitrile, and methanol high-performance liquid chromatography (HPLC) grade were purchased from LABCHEM (USA). Propylene glycol was purchased from S&C Chemicals Supplyco (UK). Normal saline 0.9% was obtained from Medochemie (Cyprus).

MATERIALS AND METHODS

Synthesis of 2-hydroxyethyl ibuprofen (HEI) [Figure 1]

A mixture of ibuprofen sodium (5.5 g, 0.024 mole) and 2-bromoethanol (3.0 g, 0.024 mole) in 20 ml dimethylformamide was stirred at 80°C for 7 h. EtOAc (40 ml) was added and the ppt was formed filtered off. The EtOAc solution was washed with H_2O (3 × 20 ml). The EtOAc was dried over anhydrous $NaSO_4$ then evaporated yielding 5.7 g (95% yield) of a colorless oily liquid.

Spectroscopy characterization

Proton nuclear magnetic resonance spectra were obtained using a Varian Unity 300 Spectrometer (Varian Medical Systems, Inc., Palo Alto, CA, USA) and chemical shift was reported as part per million (ppm) relative to internal standard, tetramethylsilane: δ 0.80 (d, 6H, j = 0.02 Hz), 1.40 (d, 3H, j = 0.02 Hz.), 1.7 (q, 1H, j = 0.02 Hz), 2.0 (s, 1H), 2.3 (d, 2Hs, j = 0.02 Hz), 3.64 (t, 2H, j = 0.01 Hz), 4.09 (t, 2H, j = 0.01), 6.98 (d, 2H, j = 0.02 Hz.), 7.09 (d, 2H, j = 0.02 Hz). Fourier transform infrared (FTIR) spectra were obtained using FTIR Spectrometer UATR Two, Li600301 spectrum made by PerkinElmer in UK: 1720 cm^{-1}. Mass spectroscopy data were obtained by GCMS-QP2010SE, Shimadzu made in Japan: 250 (M^+).

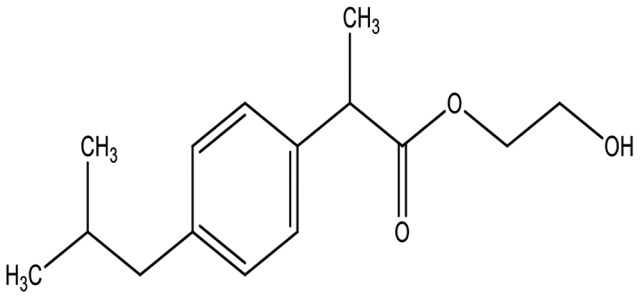

Figure 1: Structure of 2-hydroxyethyl ibuprofen

HPLC method

The concentration of HEI (prodrug) and its parent's ibuprofen was measured by Thermo Scientific Dionex Ultimate 3000 series in samples of rat's plasma and brain. The ultraviolet detection was set at a 222 nm HEI and ibuprofen. The HPLC column was C18 (4.6 × 250 mm) 5 µm.

The used mobile phase to separate each of HEI and ibuprofen composed of 20 mM phosphate buffer solution (pH 2.5) and acetonitrile in ratios of 46:54 and 55:45 for brain and plasma samples, respectively. The mobile phase was filtered and adjusted at pH 5. Loop injection volume was 30 µl and 10 µl for brain and plasma samples, respectively. The flow rate was 2 ml/min. The retention times were 10.9 min and 12.8 min for ibuprofen and HEI, respectively, in plasma samples, whereas 5.8 min and 6.18 min for ibuprofen and HEI, respectively, in brain samples [Figure 2].

Hydrolysis of HEI at different pH values

The stability of HEI was investigated at three pH values of 2.5, 5, and 7.4 in phosphate buffer solutions. The reactions were initiated by the addition of 300 µl of a 1.00 mg/ml stock acetonitrile solution of the prodrug to 5 ml of preheated buffer solution in hermetically sealed flasks. The final concentration of the prodrug was 60 µg/ml. The solution was kept in a shaking water bath at 37°C. Samples of 500 µl were taken from the solution at 0, 60, 120, and 240 min, vortexed, and put in the vial of HPLC for analysis.

Hydrolysis of HEI in rat's plasma

The rat plasma was prepared immediately before each experiment. Blood was drawn from rat through the ocular artery and collected in EP heparinized tubes which are paved with heparin sodium to prevent the clotting of samples. After that, samples were centrifuged at 5000 rpm for 10 min to isolate plasma. The resulting plasma was incubated with prodrugs without dilution at 37°C using a shaking water bath.

An amount of 300 µl of 1.00 mg/ml stock acetonitrile solution of the prodrug HEI was added to 5 ml of the incubated plasma at 37°C. The resulted final concentration is 60 µg/ml. Samples

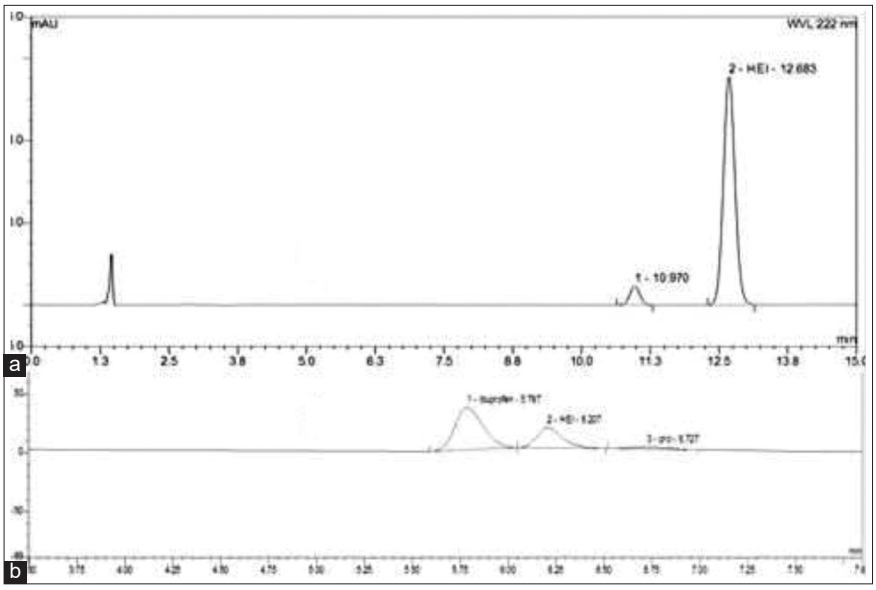

Figure 2: High-performance liquid chromatography chromatograms of hydroxyethyl ibuprofen and ibuprofen for quantifying them: (a) Under plasma conditions and (b) under brain conditions

of 400 µl were withdrawn and deproteinized by adding similar amount of acetonitrile at appropriate time points. The established mixture was vortexed then centrifuged at 11.000 rpm for 15 min, an aliquot of the supernatant was collected to be analyzed by HPLC.

Hydrolysis of HEI in rat's brain homogenate

Rats were sacrificed by decapitation. The brains were removed and homogenized with 0.9% saline (g/ml) at a ratio of 1:2 immediately before use then the homogenate was kept in shaking water bath at 37°C.

An amount of 300 µl of the 1.00 mg/ml stock solution of HEI was added to 5 ml of the incubated brain homogenate (the final concentration of 60 µg/ml for HEI), an aliquot of 500 µl was withdrawn and deproteinized by adding an equal amount of acetonitrile. After that, the mixture was vortexed then centrifuged at 11.000 rpm for 15 min, an aliquot of the supernatant was collected to be analyzed by HPLC.

Studying the kinetics of ibuprofen and HEI after ip application

Wistar male rats weighing between 200 and 250 g were used in this study. The animals were purchased originally from University of Jordan and fertilized at animal house of Isra University. All the procedures were carried out in harmony with the NIH guidelines for the care and use of laboratory animals which were approved by the Animal Ethics Committee of Isra University.

The investigated prodrug and its parent injected ip through the abdomen. For each sampling time point, three rats were treated with a single dose of either ibuprofen (50 mg/kg) or HEI (60 mg/kg).

Before administration, the compounds were dissolved in a mixed solvent containing a 1:2:2 ratio of ethanol, 0.9% saline, and propylene glycol, respectively, the injected volume of solution to each rat was 10 ml/kg.[12]

At specific time, blood samples were obtained from the ocular artery and placed into heparinized EP tube. Rats were promptly sacrificed by means of decapitation (cervical dislocation) then open the craniums and removing the brains to collect the whole brain sample, plasma was separated by centrifugation at 5000 rpm for 5 min and stored at −20°C until assay. The brain samples were removed, washed with cold saline, and weighed to homogenize with a 2-fold volume of 0.9% saline (g/ml). The homogenates were also stored at −20°C until assay. In case of brain samples, aliquots of 500 µl were added from the pre-stored plasma and brain samples to equal amount of acetonitrile for deproteinization, the mixture vortexed and centrifuged at 11.000 rpm for 15 min; finally, an aliquot of the supernatant was collected to be analyzed by HPLC method.

Pharmacokinetic and statistical analysis

All the values of concentration are triplicate and data calculated as mean ± standard deviation (SD). Comparisons between results from different groups were performed using one-way analysis of variance by the program GraphPad Prism. Statistical significance level was <0.05. The area under the concentration-time profile (area under the curve [AUC_{0-t}]), the maximal concentration (C_{max}), and the time needed to reach C_{max} (T_{max}) were calculated by Phoenix 8.1 program.

RESULTS AND DISCUSSION

HPLC analysis and calibration curve

Stock solution of each of HEI and ibuprofen was prepared in the mobile phase; then, different concentrations were prepared to establish the calibration curves of these concentrations against measured areas under the curve using HPLC method. The correlations and regression SD were calculated and the results are represented in Table 1.

Hydrolysis of HEI in the phosphate buffer solution at different pH values

Since the aim of this study is to improve the bioavailability of ibuprofen in the brain by applying prodrug approach, the prodrug under testing must pass different physiologic pH and be absorbed then pass intact from plasma through BBB and hydrolyzed in the brain. To evaluate this, the chemical hydrolysis of the prodrug in phosphate buffer was studied to predict the extent of stability at different physiologic pH (2.5, 5, and 7.4). Furthermore, the rate and extent of HEI conversion into the corresponding parent ibuprofen was studied in plasma and brain homogenate as described in methodology part.

Data fitting showed that the hydrolysis of the prodrug (HEI) according to the first-order kinetic, the first-order rate constant ($K_{hydrolysis}$), and the half-lives ($t_{1/2}$) was calculated by linear regression of Ln concentration against time in a minute and the data are represented in Table 2. The first-order rate constant ($K_{hydrlysis}$) equal to slope while the half-lives ($t_{1/2}$) obtained from this equation:

$$t_{½} = 0.693/K_{hydrolysis}$$

Based on the values in Table 2, the half-lives are 17.76, 11.00, and 5.92 in pH 2.5, 5, and 7.4, respectively, the stability of ester bond in the prodrug is inversely proportional to pH value. Hence, the prodrug HEI will be more stable at acidic pH before absorption and subject to hydrolysis in the physiological environment slowly. According to these results, it is obvious that the HEI is sufficiently stable under non-enzymatic conditions as prodrug.

The $t_{1/2}$ of HEI in plasma was 3 min, this indicates that the prodrug is susceptible to hydrolysis and thus releases quickly the ibuprofen. The regeneration of ibuprofen from its prodrug in rat's plasma was fast counter to their regeneration in rat's brain homogenate which was almost slow according to the rate constant of hydrolysis (0.882 h^{-1}) that indicates that the rate of hydrolysis of the prodrug is slow and the half-life $t_{1/2}$ (48 h) longer. This comes along with the finding of Fan *et al*. 2011. Fan *et al*. related the lower rate of hydrolysis in brain homogenate of mice than in mice's plasma for the designed prodrug of naproxen by adding glucose moiety to the shortage of esterases in brain in comparison with that in plasma.[13]

Study of ibuprofen HEI kinetics after ip administration

To assess the *in vivo* behavior and evaluate the pharmacokinetic parameters of HEI and its parent in plasma and brain, a single equimolar dose of ibuprofen (50 mg/kg) and HEI (60 mg/kg) was administered ip to a number of rats. Plasma and brain concentrations of each drug were monitored at suitable time intervals by HPLC.

The change in plasma level of HEI and its parent ibuprofen in plasma and brain over 60 min after ip injection of HEI which was quantified using HPLC-method is represented in Figure 3.

Figure 3 shows that each of HEI and ibuprofen resulted from hydrolyzing HEI appeared in plasma rapidly after 2 min of ip administration. Furthermore, only low fractions of HEI were detected in the plasma and just for 10 min. However, HEI was not detected in brain. Besides, low concentrations were detected in brain in comparison to plasma level.

Non-derivatized ibuprofen was administered ip by the same dose level to compare the results to HEI. Its plasma and brain levels are represented in Figure 4.

Figure 4 shows that ip administration of ibuprofen itself gives maximum plasma concentration three and half folds the maximum ibuprofen concentration resulted from the administration of HEI. This could be attributed to possible trapping or rapidly hydrolyzing of HEI in the peritoneum cavity before reaching the plasma. However, the observed maximum concentration (C_{max}) 32.716 µg/ml of ibuprofen after at 6.168 min, then it declined dramatically to 10.85 µg/ml during the next 10 min, after that the concentration decreased

Table 1: Concentrations, correlations, and regression standard deviation of different established calibration curves which used for analyzing ibuprofen and HEI in plasma and brain

Drug	Concentrations (µg/ml)	Correlation coefficient (R)	Regression standard deviation (SD)
Ibuprofen in brain	0.5–10	0.999	0.0084
Ibuprofen in plasma	1–25	0.999	0.029
HEI in brain	0.2–50	0.999	0.026
HEI in plasma	1–25	0.999	0.018

The data were obtained as mean (*n*=3)±SD (standard deviation). HEI: Hydroxyethyl ibuprofen

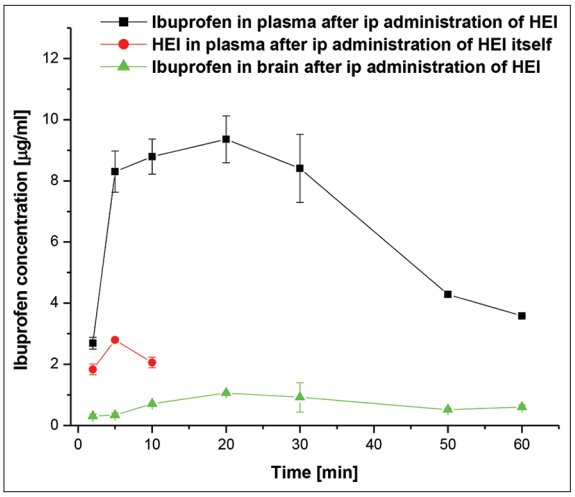

Figure 3: Plasma and brain level time curves of hydroxyethyl ibuprofen (HEI) and ibuprofen resulted from hydrolyzing HEI after intraperitoneal injection of HEI

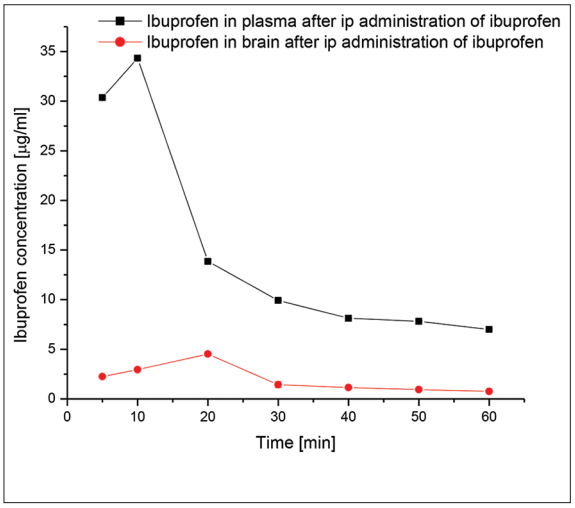

Figure 4: Plasma and brain level time curves of ibuprofen after intraperitoneal injection of ibuprofen

as a little bit. On the other hand, the maximum concentration of ibuprofen that resulted from the prodrug (HEI) in Figure 3 was 10 µg/ml after 14.2 min which is lower concentration and longer time than of ibuprofen resulted of injected ip ibuprofen itself. Furthermore, the ibuprofen raised continuously in the brain till 20 min then decline parallel to plasma level.

The AUC, elimination rate constant (K10), absorption rate constant (K10), maximum concentration (C_{max}), and time of maximum concentration (t_{max}) were estimated in plasma and brain for ibuprofen and ibuprofen resulted from hydrolysis of HEI after ip administration by Phoenix 8.1 program by applying one-compartment first-order input open model analysis. The results are tabulated in Table 3.

The results in Table 3 show that the absorption and elimination rate constants of ibuprofen and ibuprofen resulted from hydrolyzing HEI were higher in plasma than

Table 2: Stability data of HEI at 37°C after incubation in buffer with different pH, in plasma and in brain homogenate

Incubation medium	$K_{hydrolysis}$ (h^{-1})	$t_{1/2}$ (h)
pH 2.5	0.039±0.002	17.76±0.91
pH 5	0.063±0.004	11.00±0.69
pH 7.4	0.116±0.0057	5.97±0.293
Plasma	14.22±2.22	0.049±0.0076
Brain homogenate	0.882±0.00049	0.79±0.026

The data were obtained as mean (*n*=3)±standard deviation.
HEI: Hydroxyethyl ibuprofen

to that in the brain. This may be attributed to the difficulty of distribution due to the presence of BBB or resulted primarily by slowing the distribution by peritoneum from peritoneal cavity to plasma. Hence, the calculated AUCs and C_{max} for ibuprofen of HEI and injected ibuprofen in brain were lower than in plasma. Besides, the brain level of injected ibuprofen itself was lower than of ibuprofen resulted from HEI. Hence, the brain level is reflection to the plasma level. This comes along with Eriksen *et al*., 2003, finding that the ibuprofen level in brain and plasma is highly correlated to each other. Moreover, the $t_{1/2}$ of synthesized prodrug by Zhang *et al*., 2012, of dexibuprofen by adding ethanolamine were 5 and 16.2 min in plasma and brain, respectively, this resembles the finding of HEI which was 4.225 and 56.426 min in plasma and brain, respectively.[12] Furthermore, AUCs and absorption rate constants of ibuprofen and C_{max} resulted from hydrolyzing HEI were lower than ibuprofen resulted of injected ibuprofen. As the t_{max} is inversely proportional to absorption rate constant, t_{max} in plasma and brain of ibuprofen resulted of HEI as shown in Table 3 was longer than of ibuprofen after injection of parent drug. Furthermore, ratios of AUCs and K01s in brain to plasma of ibuprofen resulted of HEI and injected ibuprofen are calculated in Table 3. These ratios were higher for injected ibuprofen in comparison to ibuprofen resulted from HEI.

To understand this loss in the ip administer dose, first, the anatomy and physiology of the peritoneum must be known. The peritoneum as a membrane in the body consists of a layer of mesothelium supported by a thin layer of connective tissue.[14] Torres *et al*., 1978, found that the absorption into the systemic circulation of compounds administered ip in large volumes through peritoneal membrane in rats depends on the molecular weight, lipid-water partition coefficient (K), and dissociation constant (pKa).[15]

The logP (log [partition coefficient]) was calculated for each ibuprofen and HEI theoretically by atom/fragment contribution method to measure the extent of lipophilicity for each of them.[16] Ibuprofen had lower LogP value of 4.06 than HEI which had a value of 4.78 which means that HEI is more lipophilic than ibuprofen. Decreasing the aqueous solubility of HEI may decrease its absorption through peritoneum in

Table 3: Estimated pharmacokinetics parameters of ibuprofen using Phoenix program in plasma and brain after ip injection each of ibuprofen and HEI

Drug	AUC (h*µg/ml)	T_{max} (h)	C_{max} (µg/ml)	K_{01} (min^{-1})	K_{10} (min^{-1})
Ibuprofen in plasma	801.9±126.5	6.6±2.1	33±3.3	0.31±0.21	0.062±0.023
Ibuprofen in brain	118.1±16.6	12.6±2.2	3.2±0.28	0.123±0.081	0.049±0.029
The ratio brain/plasma	0.147			0.397	
Ibuprofen of HEI in plasma	537.2±70	14.2±1.68	10±0.62	0.143±0.044	0.028±0.0079
Ibuprofen of HEI in brain	68.12±15.3	20.96±2.5	0.99±0.068	0.083±0.044	0.024±0.0142
The ratio of brain/plasma	0.127			0.58	

The data were obtained as mean (*n*=3)±standard deviation. AUC_{0-t}: Area under the time concentration curve up to the last measurable concentration, C_{max}: Maximum concentration, T_{max}: Time at maximum concentration (C_{max}), K01: The absorption rate constant, and K10: The elimination rate constant, HEI: Hydroxyethyl ibuprofen

comparison to ibuprofen. Furthermore, the rapid hydrolysis for HEI in plasma did increase the absorption rate from plasma to brain.

Lukas *et al*., 1971, found that compounds administered ip are absorbed primarily through the portal circulation, therefore, must pass through the liver before reaching other organs.[17] Hence, when a drug distributes across the peritoneal membrane that surrounds the liver, significant metabolism may occur and this will produce an effect similar to the first-pass phenomenon following oral administration. Therefore, bioavailability may be reduced for those drugs which undergo hepatic clearance.[18]

CONCLUSIONS

In this study, a brain-targeting prodrug was synthesized by adding hydroxyethyl moiety to ibuprofen. Subsequently, its kinetics was studied in comparison to ibuprofen itself after ip administration. This is the 1st time that this moiety has been utilized in the modification of compounds for brain-targeting delivery. The HEI showed higher stability in acidic media. Furthermore, the hydrolysis of HEI was faster in plasma than in brain which may be related the complexity of the composition of plasma and the presence of different enzymes. Hence, HEI is hydrolyzed in plasma after oral absorption where remains stable in acidic media. Moreover, the distribution of ibuprofen after ip administration to the brain is elucidated. Furthermore, it could be demonstrated that the increasing in the lipophilicity of ibuprofen by esterification by adding ethylene hydroxyl group to ibuprofen did not lead to increase the diffusion of ibuprofen to the brain. Hence, it is recommended to study the diffusion to the brain of ibuprofen prodrug in future work after decreasing its lipophilicity instead of increasing the lipophilicity. The bioavailability of tested prodrug was low after ip administration due to the loss that occurs in the peritoneal. However, there are many different factors that affect the absorption of the compound from the peritoneal to plasma such as molecular weight, lipid-water partition coefficient (K), and dissociation constant (pKa).

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