Zagazig J. Pharm. Sci. June 2001
Vol. 10 , No. pp. 34 - 40

ISSN 1110- 5089

# EFFECT OF CERTAIN FACTORS ON BINDING OF KETOPROFEN TO HUMAN SERUM ALBUMIN

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## ABSTRACT

A study was made to investigate the interaction of Ketoprofen with human serum albumin (HSA) in isotonic Sorensen's phosphate buffer of pH 7.4 at 37°C. The equilibrium dialysis technique was used to assess factors influencing Ketoprofen binding to HSA. Results have demonstrated a marked binding of Ketoprofen to HSA. The binding characteristics were affected by certain factors. Increasing the concentration of the drug was accompanied by a reduction in the amount bound to HSA. While, binding of the drug with HSA was directly proportional to HSA concentration. Changing pH values had no effect on the binding of drug with HSA. Addition of three organic aliphatic acids, namely citric, tartaric and acetic acid to (HSA) did not result in significant changes in the values of binding parameters of drug to HSA. In contrast, the addition of succinic acid to albumin-Ketoprofen solution resulted in a decrease in the binding of drug to albumin.

The addition of relatively large amounts of creatinine, uric acid and phenol failed to produce a significant decrease in Ketoprofen binding.

In contrast, it has been found that urea more or less decreased Ketoprofen Binding and this decrease was concentration dependent.

Regarding the effect of guanidines on the binding of Ketoprofen to HSA, it was found that both methylguanidine, guanidinosuccinic acid guanidinoacetic acid failed to induce a significant changes in values of binding parameters.

The binding of Ketoprofen to HSA was examined in presence of four indolic compounds namely; indole-acetic acid, indican, indole-lactic acid and indole butyric acid.

It was found that all indolic compounds showed a significant decrease in Ketoprofen albumin binding and this decrease was concentration dependent. The order of inhibitory capacity was indole- lactic acid < indican < indole-acetic acid < indole-butyric acid.

## INTRODUCTION

A very large number of drugs bind to some degree to plasma proteins. The bound drug can not cross biological membranes in the body. Only the unbound fraction of drug in blood can penetrate the blood brain barrier or the gastrointestinal epithelium and undergo glomerular filtration[1]. The most important component of the blood responsible for binding is albumin which carries a negative charge at the physiologic pH and interacts with both anions and cations. In addition, the physicochemical properties of drugs play an important role in their binding to various blood components [2]. Usually, the protein-bound drug is pharmacologically inactive, since large macromolecules cannot diffuse across cell membranes. Drugs which are strongly bound to protein have a very large Ka and exists as the drug protein complex. With such drugs a large dose may be needed to obtain a reasonable therapeutic concentration of free drug [3].

Ketoprofen, a propionic acid derivative, is a nonsteroidal anti inflammatory drug. Ketoprofen is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in peri-articular disorders such as bursitis and tendinitis, in mild to moderate pain such as dysmenorrhoea or postoperative pain, and in other painful and inflammatory conditions such as acute gout or soft-tissue disorders. The usual daily dose by mouth is 100 to 200 mg in 2 to 4 divided doses with food, controlled-release formulations taken once daily may also be used. For relief of pain a dose of 25 to 50 mg every 6 to 8 hours has been suggested. Ketoprofen may also be administered rectally as suppositories in a usual dose of 100 mg at night. The total daily combined dose by mouth and by rectum should not exceed 200 mg. Ketoprofen has also been used orally, rectally, intramuscularly, and topically as the lysine salt and intramuscularly and intravenously as the sodium salt[4-7].

The aim of the present study was investigate the interaction of Ketoprofen an anti-inflammatory drug, with human serum albumin (HSA) and to determine the binding characteristics of the drug with HSA.

## EXPERIMENTAL

### Materials and Equipment :

1-Human serum albumin fraction V, molecular weight 69,000 crystallized and lyophilized. (Sigma, London Chemical Co. Ltd. England)

2-Cellulose dialysis tubings, molecular weight cut off 10,000, flat width 25mm, length 12 cm, cylinder diameter 15.9 mm, (Fisher Scientific Company, Lansburgh, Pennsylvania, 15205, U.S.A.).

3-Sorensen's phosphate buffer of pH 6.6, 6.8 and 7.4 [8]

4-U.V. spectrophotometer (Shimadzu, Japan).

5-Shaking water bath, thermostatically controlled (Astell Hearson , England ).

6-pH-meter (Gallenkamp International, Loughborough, Leicestershire, LE110TR, England).

7-Chemicals used were all of the analytical grade.

8-Ketoprofen (Amriya For Pharmaceutical Industries, Alexandria, Egypt)

### Binding Studies:

The equilibrium dialysis technique was employed for measuring and conducting binding studies. Nine pieces of cellulose dialysis tubings were cut in dimensions of 12 cm length and were soaked over night in a solution of Sorensen's phosphate buffer. The dialysis tubings were then washed several times with

the buffer., then with deionized water. They were tested for adsorption towards ketoprofen by placing 5 ml of 400 ug/ml ketoprofen in isotonic Sorensen's phosphate buffer pH 7.4 inside the dialysis tube which was immersed in a neutral glass test tube containing 20 ml. of the same phosphate buffer, after the tubes were shaken for 8 hours at 37°C to attain equilibrium, the concentration of free ketoprofen was determined spectrophotometrically at 258 nm. Also, after equilibration, the pH of the solutions inside and outside the dialysis tube were measured with a pH meter.

The pH of the solution on both sides of the dialysis tubing remained identical during incubation, indicating that no appreciable Donnan effect occurred, therefore, corrections for the Donnan effect were not made in the binding experiments. It was noted that ketoprofen had no affinity to be adsorbed on the dialysis tubings.

Nine dialytic units were prepared and used for each experiment. Each dialytic unit consists of two cells. The outer one is a test tube, contains isotonic Sorensen's phosphate buffer, pH 7.4. The cellulose dialysis tubing is introduced inside the outer cell leaving the two opened terminals outside the outer cell. This inner cell contains the drug with the albumin in isotonic Sorensen's phosphate buffer, pH 7.4. The upper opening of the outer cell was covered with a perforated rubber cover to prevent large losses of the inner solution and to keep it constant during the experimental study.

Five ml of drug with albumin in isotonic Sorensen's phosphate buffer, pH 7.4, was pipetted into the inner cell and 20 ml of the same buffer was introduced in the outer cell of the dialysis apparatus.

Each experiment was carried out at a fixed concentration of (HSA) and different concentrations of ketoprofen was used in a concentration range of 3.18 $x10^{-4}$ M to 9.54 $x10^{-4}$ M while albumin concentration was 1.45 x $10^{-4}$ M.

The dialytic units were allowed to be rocked in a shaker water bath previously adjusted at 37 ±1°C and at a speed of 60 r.p.m. till equilibrium was reached (4 hours). The solution of the outer cell was centrifuged and the amount of free drug outside the dialysis tube (which equals that inside) was determined spectrophotometrically at 258mm using isotonic Sorensen's phosphate buffer pH 7.4 as a blank.

## RESULTS AND DISCUSSION

The equilibrium time for binding of Ketoprofen with (HSA) was estimated and from the results obtained, it was found that equilibrium was established within 4 hours [Figure (1) ]

Equilibrium dialysis data for Ketoprofen binding to HSA in isotonic Sorensen's phosphate buffer (pH 7.4) at 37°C were plotted according to scatchard [9] shown in figure 2 The non-linearity of the Scatchard plot indicates that more than one type of binding site is involved in the interaction between the drug and albumin.

The number of primary binding sites (n) and association constant (Ka)can be calculated from the equation:

$$1/r = 1/nKa\,(D) + 1/n$$

Where (D) is the molar concentration of the free drug and (r) is the number of moles of the drug bound per mole of albumin. The high value of the association constant K ($6.363 \times 10^{-4}$M) indicates that the drug has a high affinity to HSA .

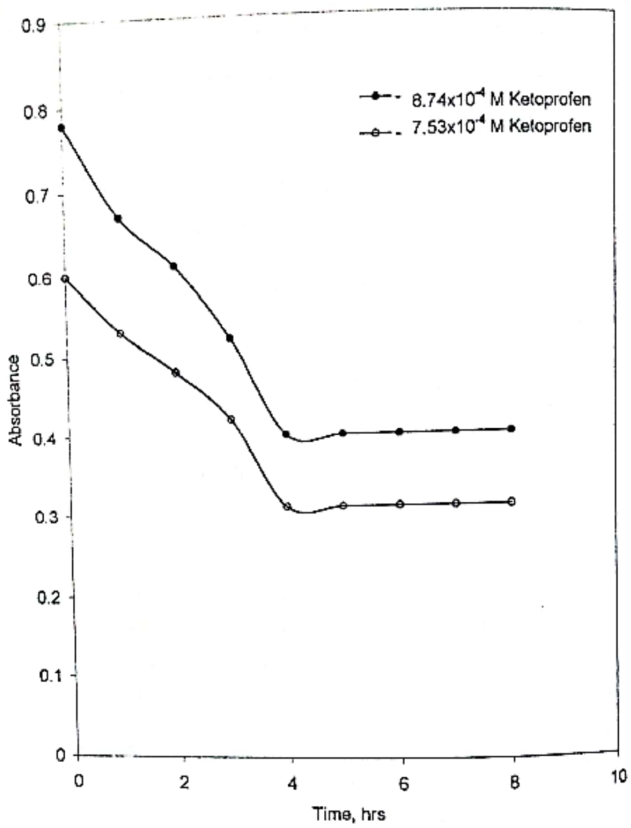


Fig. (1) The Equilibrium Time For The Binding of Ketoprofen To Human Serum Albumin.

Table 1 shows that the percent of drug bound to (HSA) depends on the total drug concentration, i.e. at a fixed protein concentration, the binding of Ketoprofen to HSA is inversely proportional to total drug concentration. This could be due to the saturation of binding sites at high drug concentrations. This conclusion is in agreement with **Mahdy** [10] who found that, at a fixed protein concentration, the percentage of ibuprofen bound to human serum albumin decreases as the drug concentration increases.

At a fixed drug concentration, it was found that the value of $K_1$ and $K_2$ increased with increasing the albumin concentration as shown in Table 2. The finding is expected because the number of binding sites increases as the albumin concentration increases. **Klotz et al.** [11] reported that the binding capacity of serum albumin decreases in liver diseases because the synthesis of albumin decreases leading to a reduction in serum albumin level. Hyperthyrodism also markedly

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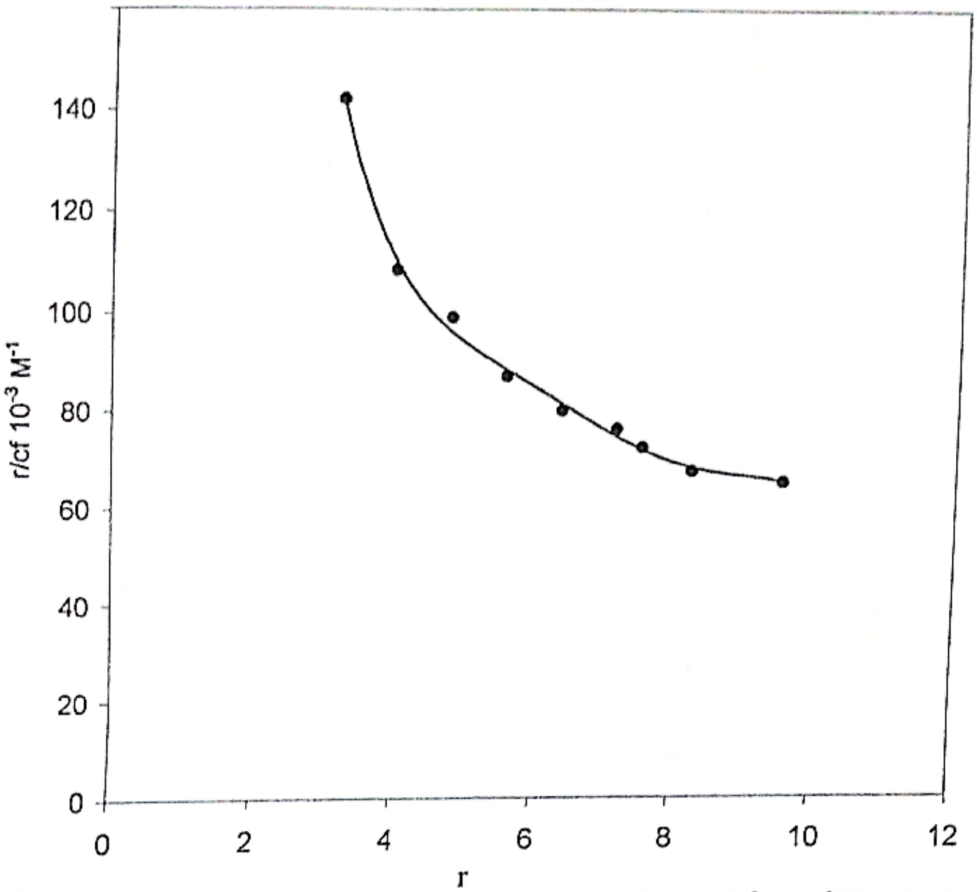


Fig. (2) : Scatchard plot of dialysis data for the binding of ketoprofen to human serum albumin in isotonic sorensen's phosphate buffer of pH 7.4 at 37°C±1.

Table (1): Binding of ketoprofen to HSA in isotonic sorensen's phosphate buffer (pH 7.44) at 37°C as a function of the drug concentration (protein concentratio 1.45 x $10^{-4}$ M).

| Initial ketoprofen Conc x $10^{-4}$ M | Bound drug x $10^{-4}$ M | % drug bound |
|---|---|---|
| 3.18 | 3.05 | 95.91 |
| 3.97 | 3.74 | 94.21 |
| 4.77 | 4.47 | 93.71 |
| 5.56 | 5.16 | 92.81 |
| 6.36 | 5.86 | 92.14 |
| 7.15 | 6.54 | 91.47 |
| 7.95 | 7.25 | 91.19 |
| 8.74 | 7.91 | 90.50 |
| 9.54 | 8.56 | 89.73 |

reduces albumin concentration and has been shown to decrease the binding of propranolol[12] .This conclusion is in agreement with that of **Woo and Greenblatt** [13] who working on the binding of quinidine to HSA.

Table 3 shows that the binding of Ketoprofen to HSA is not affected by pH change from 6.6 to ,7.4. This finding is not in agreement with that observed by **Mahdy et al.** [10] where they demonstrated an increase in binding of azapropazone with (HSA) as pH increase due to conformational changes occurred in HSA over pH from 6 to 9 and known as N to B or B to N transition which affects the binding of drug to HSA.

Table (2) : Binding parameters for the interaction between ketoprofen and different human serum albumin concentrations in isotonic Sorensen's phosphate buffer of (pH 7.4) at 37°C calculated from scatchard Plot.

| Human serum albumin Conc. | $K_1$x$10^{-4}$ M | n1 | $K_2$x$10^{-4}$ M | n2 |
|---|---|---|---|---|
| 1.45X$10^{-4}$M | 6.363 | 4.01 | 1.401 | 5.32 |
| 2.17X$10^{-4}$M | 10.184 | 2.71 | 2.989 | 2.14 |
| 2.90X$10^{-4}$M | 13.291 | 2.29 | 3.359 | 2.38 |

Drug concentration from 3.18 x $10^{-4}$ M to 9.54 x $10^{-4}$ M

Table (3): Binding parameters for the interaction between ketoprofen and $1.45 \times 10^{-4}$M human serum albumin concentration in isotonic sorensen's phosphate buffer of different pH values at 37°C ±1 as drived from scatchard plot.

| PH | $K_1 \times 10^{-4}$ M | n1 | $K_2 \times 10^{-4}$ M | n2 |
|---|---|---|---|---|
| 6.6 | 6.276 | 4.03 | 1.334 | 5.53 |
| 6.8 | 6.289 | 4.04 | 1.334 | 5.52 |
| 7.4 | 6.363 | 4.01 | 1.401 | 5.32 |

Drug concentration from $3.18 \times 10^{-4}$ M to $9.54 \times 10^{-4}$ M

Table (4) illustrate the effect of succinic acid on the binding of (HSA). The presence of succinic acid appears to decrease the binding of the drug to (HSA ). The value of K decreased from $4.418 \times 10^{-4}$ M to 3.209 $\times 10^{-4}$M as the concentration of succinic acid increased from $5 \times 10^{-4}$ M to $5 \times 10^{-4}$ M. Citric acid, acetic, acid and tartaric acid appear to have no effect on the binding of ketoprofen to (HSA). This finding is in agreement with **Abd-Elbary** [14] who working on the binding of pipazethate-HCl to (HSA). The author found that all the aforementioned acids decrease the binding of the drug to (HSA). **Ballou and Coworkers** [15] reported competition for binding between phosphate ions from the buffers and other anions by interacting with the same site on the protein molecule. A similar observation was reported by **Teresi and Luck** [16] .

In renal failure and uremia, various endogenous metabolic products known as "uremic toxins" accumulate in the blood. In order to investigate the participation of these in the drug-protein binding defect, some were tested for their ability to inhibit Ketoprofen HSA binding.

Binding of ketoprofen to human serum albumin was found to be unaffected by the presence of four suspected uremic toxins namely, urea, creatinine, uric acid and phenol. The addition of relatively large amounts of creatinine , uric acid and phenol failed to produce a binding defect for ketoprofen. On the other hand, the combination of urea, creatinine, uric acid and phenol at their maximum concentration exhibited a noticable defect in Ketoprofen-human serum albumin binding as shown in Table (5) and Table (6). Urea, the mostly incriminated uremic toxin, showed a more or less considerable decrease in binding of ketoprofen to HSA and the decrease was drug-concentration dependent. **Craig et al** [17] has shown that the addition of relatively large amounts of creatinine, urea, uric acid and phosphate to normal or charcoal-treated uremic serum failed to produce a binding defect for sulphamethoxazole. **Campian et al.**[18] stated that, neither singly nor in combination, did urea, creatinine uric acid or phenol cause a decrease in binding. Also, **Ikeda et al.,** [19] found that urea and creatinine did not affect frusemide bovine serum albumin binding.

The binding of ketoprofen to human serum albumin was reduced in presence of four indolic compounds namely: indole acetic acid, indican.. indole lactic acid and indole butyric acid. Further decrease was also noticed with increasing indole concentration, these results are illustrated in Table (7). In spite of the increase in the binding capacity with increasing indole concentration, the decrease in the binding may be due to the great decrease in the data proved lhat all indole derivatives inhibit the binding competitively and the order of the inhibitory capacity was indole lactic acid < indican < indole acetic acid < indole butyric acid. It was also found that those indole derivatives showed concentration -dependent inhibition. Thus indole derivatives may be candidates, which cause the decrease of ketoprofen to albumin binding. This finding is in agreement with that of **Ikeda et al.**[19] working on the binding of frusemide to bovine serum albumin.

Table (4) : Binding parameters for the interaction between ketoprofen and $1.45 \times 10^{-4}$M human serum albumin in presence of different concentrations of aliphatic acids at 37°C ±1 calculated from scatchard plot.

| Aliphatic acid Conc. (M) | $n_1$ | $K_1 \times 10^{-4}$ M | $n_2$ | $K_2 \times 10^{-4}$ M |
|---|---|---|---|---|
| $5.00 \times 10^{-4}$M Citric acid | 3.88 | 6.789 | 5.18 | 1.466 |
| $15.00 \times 10^{-4}$ M Citric acid | 3.92 | 6.68 | 5.28 | 1.431 |
| $5.00 \times 10^{-4}$ M Tartaric acid | 3.96 | 6.432 | 5.52 | 1.364 |
| $15.00 \times 10^{-4}$ M Tartaric acid | 4.02 | 6.208 | 5.48 | 1.360 |
| $5.00 \times 10^{-4}$ M Acetic acid | 4.85 | 6.952 | 5.41 | 1.415 |
| $15.00 \times 10^{-4}$ M Acetic acid | 3.96 | 6.627 | 5.54 | 1.359 |
| $5.00 \times 10^{-4}$ M Succinic acid | 4.44 | 4.418 | 5.46 | 1.205 |
| $15.00 \times 10^{-4}$ M Succinic acid | 4.95 | 3.209 | 5.55 | 1.054 |

Drug concentration from $3.18 \times 10^{-4}$ M to $9.54 \times 10^{-4}$ M

Table (5) : Binding parameters for the interaction between ketoprofen and $1.45 \times 10^{-4}$M human serum albumin in presence of different concentrations of urea, creatinine, uric acid and phenol at 37°C calculated from scatchard Plot.

| Uremic toxin (M) | $n_1$ | $K_1 \times 10^{-4}$ M | $n_2$ | $K_2 \times 10^{-4}$ M |
|---|---|---|---|---|
| (1) $33.00 \times 10^{-3}$ urea | 4.08 | 5.813 | 3.61 | 1.343 |
| $67.00 \times 10^{-3}$ urea | 4.12 | 5.582 | 5.42 | 1.325 |
| (2)$5.95 \times 10^{-3}$ uric acid | 3.97 | 6.440 | 5.47 | 1.371 |
| $23.79 \times 10^{-3}$ uric acid | 4.01 | 6.226 | 5.33 | 1.396 |
| (3) $8.84 \times 10^{-3}$ creatinine | 3.86 | 6.740 | 5.61 | 1.355 |
| $44.20 \times 10^{-3}$ creatinine | 4.03 | 6.111 | 5.14 | 1.436 |
| (4) $2.13 \times 10^{-3}$ phenol | 3.97 | 6.440 | 5.37 | 1.396 |
| $10.63 \times 10^{-3}$ phenol | 4.01 | 6.226 | 5.26 | 1.413 |
| (5)Combination of 1-4 at maximum conc. | 4.27 | 4.991 | 5.42 | 1.272 |

Drug concentration from $3.18 \times 10^{-4}$ M to $9.54 \times 10^{-4}$ M

Table (6) : Limiting binding capacities (mole/gm) for the interaction between Ketoprofen and $1.45 \times 10^{-4}$ M human serum albumin in presence of different concentration of urea , creatinine, uric acid and phenol in isotonic Sorensen's phosphate buffer of pH 7.4 at 37°C ±1.

| Uric toxin concentration (M) | Limiting binding capacity (mole /gmx $10^{-5}$ |
|---|---|
| (1) $33.00 \times 10^{-3}$ urea | 10.40 |
| $67.00 \times 10^{-3}$ urea | 10.51 |
| (2)$5.95 \times 10^{-4}$ uric acid | 10.20 |
| $23.79 \times 10^{-4}$ uric acid | 10.12 |
| (3) $8.84 \times 10^{-4}$ creatinine | 10.37 |
| $44.20 \times 10^{-4}$ creatinine | 10.11 |
| (4) $2.13 \times 10^{-4}$ phenol | 9.81 |
| $10.63 \times 10^{-4}$ phenol | 10.11 |
| (5)Combination of 1-4 at maximum conc. | 10.79 |

Drug concentration from $3.18 \times 10^{-4}$ M to $9.54 \times 10^{-4}$ M

Binding of ketoprofen to human serum albumin was found to be unaffected by the presence of guanidines which are incriminated to be uremic toxins. Binding parameters were calculated and presented in Table (8). The obtained data proved that neither methyl guanidine and , guanidinoacetic acid nor guanidinosuccinic acid cause a decrease in the binding of ketoprofen to human serum albumin. Similar results were obtained by **Graig et al.** [20] who stated that excessive quantities of methylguanidines, guanidinosuccinic acid and guanidinoacetic acid failed to produce a defect in the binding of sulfamethoxazole with sera of normal individuals. This finding also is in agreement with that of **Ikeda et al.**[19] who certified that guanidinoacetic acid and guanidinosuccinic acid did not affect frusemide binding to Bovine serum albumin.

Table (7) : Binding parameters for the interaction between ketoprofen and $1.45 \times 10^{-4}$M human serum albumin in presence of different concentrations of Indole derivatives at 37°C calculated from scatchard Plot.

| Indole Derivative Conc. (M) | $n_1$ | $K_1 \times 10^{-4}$ M | $n_2$ | $K_2 \times 10^{-4}$ M |
|---|---|---|---|---|
| $1.00 \times 10^{-3}$ indole lactic acid | 4.52 | 4.156 | 5.47 | 1.181 |
| $1.5 \times 10^{-3}$ indole lactic acid | 4.79 | 3.487 | 5.99 | 1.096 |
| $1.00 \times 10^{-3}$ indican | 4.90 | 3.311 | 5.50 | 1.078 |
| $1.50 \times 10^{-3}$ indole | 5.30 | 2.734 | 5.48 | 0.999 |
| $1.00 \times 10^{-3}$ indole acetic acid | 5.40 | 2.617 | 5.49 | 0.980 |
| $1.50 \times 10^{-3}$ indole acetic acid | 5.93 | 2.140 | 5.39 | 0.907 |
| $1.00 \times 10^{-3}$ indole butyric acid | 6.03 | 2.064 | 5.40 | 0.891 |
| $1.50 \times 10^{-3}$ indole butyric acid | 6.68 | 1.703 | 5.19 | 0.829 |

Drug concentration from $3.18 \times 10^{-4}$ M to $9.54 \times 10^{-4}$ M

Table (8) : Binding parameters for the interaction between ketoprofen and $1.45 \times 10^{-4}$M human serum albumin in presence of 20 mg/100ml Guanidines at 37°C calculated from Scatchard Plot.

| Guanidine conc. 20 mg/100 ml | $n_1$ | $K_1 \times 10^{-4}$ M | $n_2$ | $K_2 \times 10^{-4}$ M |
|---|---|---|---|---|
| Methyl Guanidine | 4.01 | 6.289 | 5.34 | 1.394 |
| Guanidinosuccinic acid | 4.02 | 6.263 | 5.33 | 1.392 |
| Guanidinoacetic acid | 4.02 | 6.250 | 5.33 | 1.394 |

Drug concentration from $3.18 \times 10^{-4}$ M to $9.54 \times 10^{-4}$ M

## CONCLUSION

From the previously obtained results, it can be concluded that ketoprofen was strongly bound to $1.45 \times 10^{-4}$M human serum albumin. The primary association constant was $6.363 \times 10^{-4}$ M .

The degree of ketoprofen binding was found to be directly proportional to HSA concentration and inversely proportional to the initial concentration.

It was found that pH did not affect the binding of ketoprofen to HSA.

Addition of citric acid, tartaric acid and acetic acid failed to produce a significant fall in the ketoprofen . HSA binding on the other hand, succinicacid exhibited a significant decrease in the drug binding and this decrease was drug-concentration dependent.

The suspected uremic toxins, creatinine , uric acid and phenol showed no affinity for competition with ketoprofen to HSA. In contrast, urea showed a more or less small decrease in ketoprofen binding to HSA and the decrease was drug-concentration dependent. It was observed that the combination of urea, creatinine, uric acid and phenol caused a remarkable defect in binding of ketoprofen to HSA.

Addition of methylguanidine, guanidinosuccinic acid and guanidinoacetic acid failed to decrease the binding of Ketoprfen to HSA.

Four indole derivatives, indole acetic acid, indole butyric acid, indole lactic acid and indican exhibited a significant decrease in the binding of Ketoprfen to HSA. These indole derivatives showed concentration-dependent inhibition and the order of decreasing binding affinity was indole lactic acid < indican < indole acetic acid < indole butyric acid.

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**Received 8 / 1 / 2001**
**Accepted 20 / 3 / 2001**

Zagazig J. Pharm. Sci. June 2001
Vol. 10 , No. pp. 34 - 40

الملخص العربى

# تأثير عوامل معينة على ارتباط الكيتوبروفين مع زلال المصل الآدمى

محمود عبدالغنى مهدى

قسم الصيدلانيات - كلية الصيدلة - جامعة الزقازيق

تم فى هذا البحث دراسة ارتباط عقار الكيتوبروفين مع زلال المصل الآدمى فى محلول الفوسفات المنظم متساو التوتر ذو أس أيدروجينى ٤ ، ٧ عند ٣٧ ° م وقد تم استخدام طريقة الديلزة المتوازنة لدراسة الأرتباط والعوامل التى تؤثر عليه وقد أوضحت النتائج ارتباط ملحوظ بين الكيتوبروفين وزلال المصل الآدمى وثبت أن ارتباط العقار يقل بزيادة تركيزة وذلك عند درجة تركيز ثابته من زلال المصل الآدمى بينما لا يوجد تأثير للأس الأيدورجينى . وقد أوضحت الدراسة أن اضافة كل من حامض الستريك وحامض الطرطريك وحامض الخليك لم تؤثر على قابلية العقار للأرتباط مع زلال المصل الأدمى فى حين أن حامض السكنيك أظهر قدرة واضحة على تقليل الأرتباط كما أنه لم يظهر تأثيرملحوظ على ارتباط العقار مع زلال المصل الآدمى بزيادة تركيز كل من الكرياتنين وحمض اليوريك والفينول بينما قل الأرتباط فى وجود اليوريا كما أوضحت الدراسة عدم وجود تأثير للجوانيدنات على ارتباط العقار. وقد تم دراسة تأثير بعض مركبات الأندول على العقار مع زلال المصل الآدمى ووجد أن جميع هذه المركبات التى أضيفت قد قللت من ارتباط الكيتوبروفين مع زلال المصل الآدمى على النحو التالى :

أندول حامض البيوتريك > اندول حامض الخليك > الانديكان > اندول حامض اللاكتيك .