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Adsorption Behaviors of Indomethacin on Cholestyramine Resin

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콜레스티라민 수지에의 인도메타신 흡착

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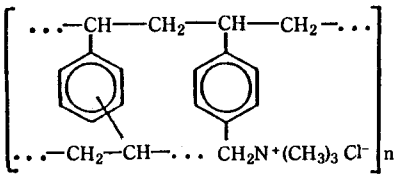
In vitro studies were performed on the interaction of indomethacin with cholestyramine, a hypocholesterolemic substance. Cholestyramine showed a marked affinity for indomethacin among tested acidic drugs and the intensity of adsorption was dependent on pH, temperature and sodium chloride. Moreover, the combination of indomethacin with some acidic drugs that formed complexes with cholestyramine, considerably inhibited the adsorption of indomethacin on the resin.

Keywords—indomethacin; cholestyramine; adsorption; adsorption inhibition; adsorptive detoxicant

It is known that cholestyramine is an anionic exchange resin containing insoluble quaternary ammonium-chloride salts. The site for anionic exchange is trimethylbenzylammonium group in the styrene/divinyl benzene copolymer (Scheme 1).



Scheme 1—Cholestyramine

The main pharmacological action of cholestyramine is the complex formation with bile salts in the small intestine.[1,2] This complex formation results in the increase of excretion into the feces,[3] and inhibits enterohepatic recirculation,[4] thus induces the reduction of intestinal absorption of both cholesterol and lipid. Therefore, cholestyramine has been used as a therapeutic agent for biliary cirrhosis, hyperlipidemia and hypercholesterolemia.[6]

These findings indicate the possible interaction between some acidic drugs and the resin in the GI tract. Drugs such as phenylbutazome, chlorothiazide, fusidic acid and naproxen showed a remarkable reduction in intestinal absorption.[7-9] The resin has also been utilized as an acute detoxicant of acetaminophen, aspirin and lincomycin,[10-12]

The purpose of this work is to investigate the possible interaction of cholestyramine with indomethacin, a nonsteroidal antiinflammatory agent, and to study the effect of some factors on the adsorption of indomethacin for the development of possible adsorptive detoxicant using the cholestyramine.

EXPERIMENTAL

Materials

Indomethacin (Shinjun, KP IV), cholestyramine (Sigma, U.S.A.), salicylic acid (Sigma, U.S.A.), phenylbutazone (Whaduk, KP IV), probenecid (Sigma, U.S.A.), nalidixic acid (Keyang, KP IV)

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phenobarbital (Shinjun, KP IV), ethacrynic acid (Sigma, U.S.A.), tolbutamide (Sigma, U.S.A.) and ibuprofen (Dongil, KP IV) were used without further purification. Other materials were reagent grade.

Adsorption of Indomethacin on Resin

The adsorption of the drug on the resin was determined by treating 10 mg of cholestyramine with 50 m*l* of 10^{-3}M indomethacin aqueous solution. The suspensions were shaken at a constant speed at 37 ± 1 °C for 1 hr to reach equilibrium. After centrifugation of the suspension, the concentration of indomethacin at equilibrium in the supernatant was determined spectrophotometrically (Pye Unicam SP8-100 type uv-vis spectrophotometer). The amount of drug adsorbed on the resin was calculated from the difference between the initial concentration and the equilibrium concentration.

In order to obtain the Langmuir isotherm, the effect of drug concentration on the adsorption was studied. The concentration of indomethacin was 0.022, 0.035, 0.039, 0.044, 0.058, 0.064 and 0.071 mEq. in 150 m*l* of phosphate buffer (pH 7.1). 10 mg of cholestyramine was added to the solutions using the same method as described in the previous section. pH ranges of buffer solutions were pH 3.0-5.0 and pH 6.0-8.0 for 0.1 M citric acid-0.2M Na_2HPO_4 solution and 1/15M NaH_2PO_4-1/15M Na_2HPO_4 solution, respectively.

Release of Indomethacin from Resin

Release study was carried out using dialysis bags of 10 cm in length containing 50 mg of drug and 800 mg of cholestyramine in 15 m*l* of artificial gastric juice (0.2% NaCl, 0.78% HCl, pH 1.7). The dialysis bags were placed in a glass cylinder containing 100 m*l* of gastric juice at 37 ± 1 °C at 100 rpm. The amounts of drug dialysed were determined by 15 min intervals for 3.5 hr.

The experiment was also carried out with 15 m*l* of artificial enteric juice (0.6% Na_4HPO_4 + 0.17% $NaH_2PO_4 \cdot 2H_2O$ solution, pH 6.8), 50 mg indomethacin and 800 mg of cholestyramine.

The dialysis rate of indomethacin in the absence of resin was also determined under the same conditions using gastric and enteric fluids.

Table I—*Adsorption Behavior of 10mg of Resin to Some Acidic Drugs (10^{-3} Mole at 37 ± 1 °C).*

Drug	Ce(mM/*l*)	% Adsorbed
Salicylic acid	0.84	16
Probenecid	0.79	21
Phenylbutazone	0.76	24
Ibuprofen	0.95	5
Indomethacin	0.60	40
Nalidixic acid	0.99	1
Phenobarbital	0.97	3
Ethacrynic acid	0.67	33
Tolbutamide	0.93	7

RESULTS AND DISCUSSION

Adsorption Behavior of Some Acidic Drugs

Since cholestyramine is quaternary ammonium anionic exchange resin, the interactions with anionic drugs is expected. The adsorption of cholestyramine with some acidic drugs was investigated.

As shown in Table I, the various acidic drugs demonstrated considerable differences in the adsorption on the resin. This fact probably results from vertical arrangement of drugs as well as anionic residue.

Attemps were made to determine various factors affecting on the adsorption of indomethacin showing the strongest adsorption capacity among the tested drugs.

pH Effect

Since drugs may interact by ionic exchange mechanism, the pH of solution can be a significant factor. Interaction between drug and resin did not occur at pH 3.0 as shown in Fig. 1. In contrast 60% adsorption at pH 5.0 and 100% adsorption between at pH 6.0 and 8.0 were observed. These results lead to the conclusion that complex formation of indomethacin (pKa 4.5) with the resin is greatly related to degrees of ionization.

Adsorption Isotherm

10 mg of resin was added to the solution having various concentrations of drug and the adsorption

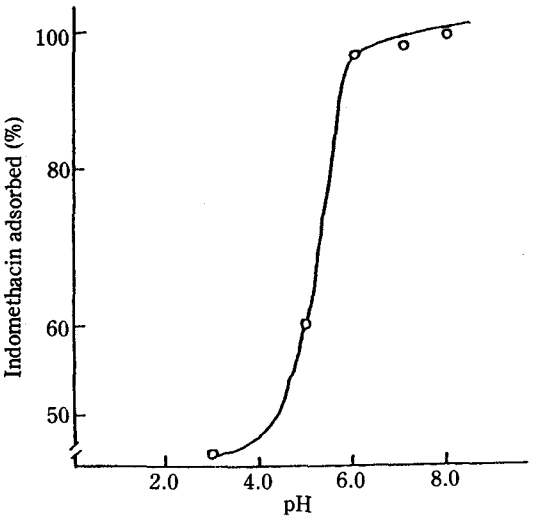

Figure 1—Influence of pH on the adsorption of indomethacin on the resin (0.10mEq of drug with 10mg of cholestyramine in 50 m*l*) at 37 ± 1 °C.

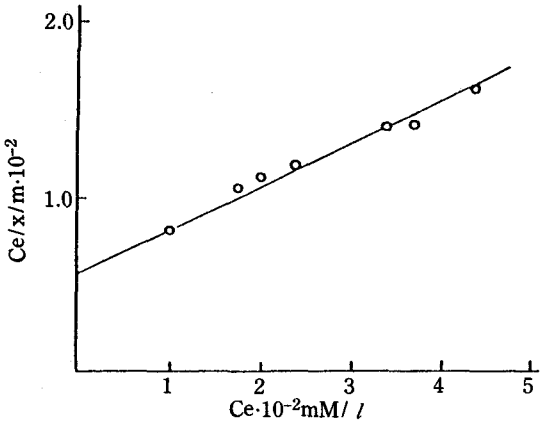

Figure 2—Langmuir adsorption isotherm of indomethacin on the resin.

was examined.

Fig. 2 shows the drug concentration at equilibrium as a function of the amount adsorbed using the Langmuir equation[13]: a linearity was obtained indicating a Langmuir-type adsorption isotherm within the tested concentration range. The results suggest that the system approaches its peak capacity for monomolecular exchange of the resin by drug. Furthermore, the strong adsorption capacity observed even at high concentration suggests that cholestyramine can be a good adsorptive detoxicant for indomethacin.

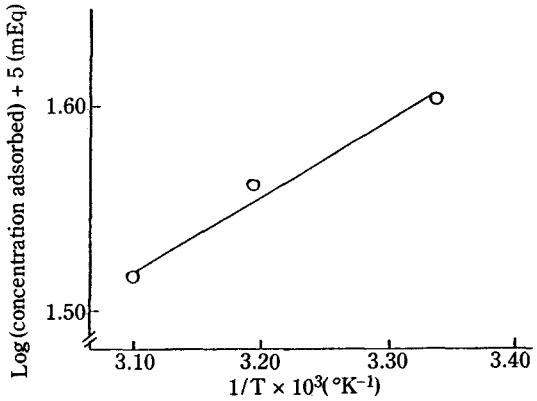

Figure 3—Effect of temperature on indomethacin concentration adsorbed on the resin.

Table II—*Effect of Sodium Chloride on Drug Adsorption Capacity of Resin at 37 ± 1 °C.*

Additives	% Adsorbed
None	36.8
100mg Sodium chloride	36.3
500mg Sodium chloride	30.0
1000mg Sodium chloride	23.4

Temperature effect on the adsorption was investigated at 25, 40 and 50 °C. As shown in Fig. 3, the increase of adsorptive capacity with temperature decrease was observed. This is caused by the fact that the adsorption is an exothermic reaction.

Effect of Sodium Chloride Concentration

Since the cholestyramine-indomethacin interaction occurs electrostatically, the chloride ions of the resin may be exchanged with the drug anions. The interaction takes place between the carboxyl group of the ionized drug and the quaternary ammonium group of the resin. Based on this fact, sodium chloride was added to resin-drug suspension of various concentrations, and the effect of sodium chloride on the drug adsorptions was examined.

As shown in Table II, addition of 100 mg of sodium chloride showed no effect. However, addition of 500 mg of sodium chloride decreased adsorption by 6% and 1,000 mg of sodium chloride by 13%. This result indicates the common ion effect of chloride ion reducing the resin-drug interaction and inhibiting the dissociation of cholestyramine.

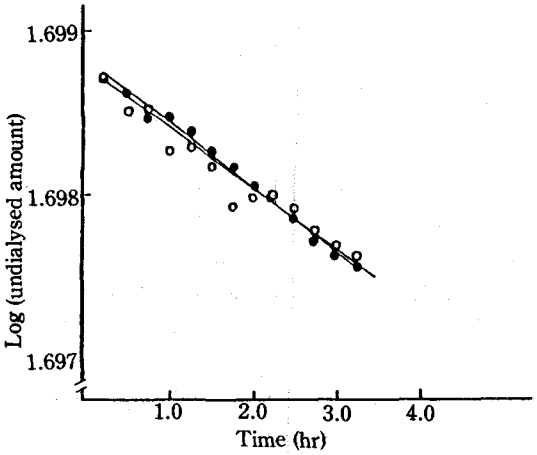

Figure 4—Amounts of undialysed indomethacin as a function of time at pH 1.7 in the absence(●) and presence(○) of cholestyramine at 37 ± 1 °C.

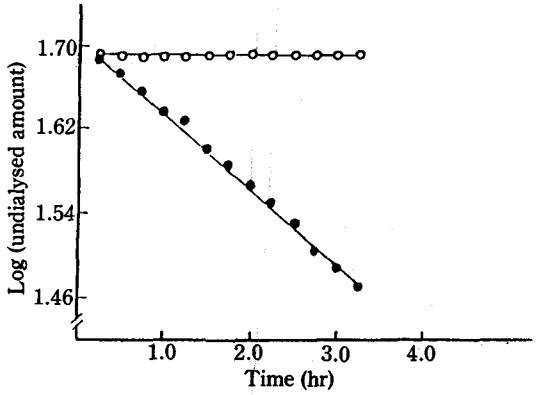

Figure 5—Amounts of undialysed drug as a function of time at pH 6.8 in the absence(●) and presence(○) of cholestyramine at 37 ± 1 °C.

Drug Release from Drug-Resin Complex

With the aim of elucidating the possible interaction of these two agents in the GI tract, release rate of indomethacin was investigated in the presence and absence of cholestyramine at pHs of the gastric and intestinal media.

Fig. 4 shows the amounts of undialysed indomethacin at pH 1.7 in the presence and absence of the resin. The presence of the resin showed no significant difference in the amounts of dialysed indomethacin. The dialysis processes followed first-order kinetics. Both the cases showed a very low and identical release rate constant of 1.66×10^{-3} hr^{-1}. This is probably due to the fact that at pH 1.7, the drug is in its unionized form, thereby limiting the interaction with the resin.

Table III—*Change in Adsorption Property of Indomethacin by Cholestyramine in the Presence of Probenecid, Ethacrynic Acid and Phenylbutazone.*

Adjuvants	Amount adsorbed (10^3M)	Inhibition(%)
Indomethacin	0.350	0
Indomethacin + Probenecid	0.254	14.0
Indomethacin + Ethacrynic acid	0.176	35.1
Indomethacin + Phenylbutazone	0.304	13.1

Fig. 5 shows the amounts of undialyzed drug as a time function in the presence and absence of the resin at pH 6.8. Significant difference was observed as compared with those obtained at pH 1.7. The release kinetics in the absence of the resin followed a first-order process. Release rate constant (0.6146 h^{-1}) is much greater than that at gastric pH resulting from varying drug solubility with pH. The presence of the resin decreases the dialysis capacity of indomethacin. Thus, in the absence of resin, 50% of the drug was dialysed over a period of 3.5 hr, while in its presence only 2% was dialysed. Since the drug is totally ionized at the intestinal pH forming a complex with the resin, the dissolution rate is thereby limited by the release of indomethacin from the formed complex.

Combination Effect

Co-administration of indomethacin with another agents possibly affects the interaction in the GI tract, thereby decreasing bioavailability. In order to determine the effects of co-administered drugs on adsorption capacity of the resin, several drugs were tested from possible competitive interaction with the resin. As shown in Table III, the decrease in the adsorption of indomethacin was greater in the case of co-administration than indomethacin alone: probenecid 14%, phenylbuta-

zone 14%, and ethacrynic acid 35%.

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