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ADSORPTION OF CERTAIN ORAL HYPOGLYCAEMICS ON KAOLIN AND CHARCOAL AND ITS RELATIONSHIP TO HYPOGLYCAEMIC EFFECTS OF DRUGS

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SUMMARY

The adsorption of acetohexamide, tolazamide and tolbutamide at pH 7.4 on kaolin and activated charcoal was studied at 37°C. Langmuir adsorption isotherms were established and the maximum adsorption capacities of activated charcoal and kaolin were estimated. The results of desorption experiments suggested that desorption was incomplete, but to a relatively greater extent from activated charcoal than from kaolin. The hypoglycaemic activity of the 3 drugs was suppressed in the presence of both activated charcoal or kaolin.

INTRODUCTION

Solid adsorbents, such as activated charcoal and kaolin have been found to interfere with the drug absorption resulting in a decrease in the bioavailability of co-administered drugs. In vivo animal studies have shown that activated charcoal reduced the gastrointestinal absorption of promazine (Sorby, 1965), aspirin, salicylamide and phenylpropanolamine (Tsuchiya and Levy, 1972), diphenoxylate (Sanvordeker and Dajani, 1975) as well as other substances. The adsorption of certain psychoactive drugs on charcoal has been compared by Sellers et al., 1977. Kaolin was found to reduce the bioavailability of lincomycin (McCall et al., 1967, McGehee et al., 1968) and digoxin (e.g. Albert et al., 1978), as well as other drugs. The decreased bioavailability under the influence of these adsorbents is brought about by adsorption of the co-administered drug on the surface of the adsorbent, thus preventing the adsorbed fraction of the drug from permeating through the GI mucosa into the blood stream.

Oral hypoglycaemics, such as acetohexamide, tolazamide, and tolbutamide are examples of the long-term drugs whose co-administration with kaolin or charcoal is most probable. It was of interest, therefore, to explore the in vitro availability of these oral hypoglycaemics in the presence of activated charcoal or kaolin, and to assess its relationship to the pharmacological activity of these drugs in vivo. Hypoglycaemic activity of the drugs was taken as measure for their pharmacological effect in rats.

METHODS

In vitro adsorption studies were carried out by dissolving acetohexamide [1], tolazamide [2] and tolbutamide [3] in phosphate buffer at pH 7.4. Fifty milliliters of solution containing 5–50 mg of the drug was placed in a 100-ml stoppered conical flask, containing activated charcoal U.S.P. XVII [4] or treated kaolin [5] (99.5% passes a 325-mesh screen) (2%). The drug–adsorbent suspension was equilibrated at 37 ± 0.2°C and shaken continuously for sufficient time to reach equilibrium (≃24 h). The suspensions were filtered [6] (those containing activated charcoal) or rapidly centrifuged, (those containing kaolin) and the clear liquid obtained was assayed spectrophotometrically [7] at 245 nm for acetohexamide, 262 nm for tolazamide and 226 nm for tolbutamide. Appropriate control solutions were also run and assayed to ensure control over experimental conditions. The amounts of each drug adsorbed on each one of the adsorbents was determined from a constructed Beer's law standard curves.

Description of the adsorbed drugs was determined at 37 ± 0.2°C in pH 7.4 phosphate buffer over 3 h as previously outlined (Khalil, 1974).

Measurement of blood glucose in rats. The effect of orally administered acetohexamide, tolazamide and tolbutamide with and without the adsorbents on blood glucose of male albino rats was investigated. Rats weighing 180–260 g were fasted 24 h before the experiment, but allowed free access to water. The animals were divided into 9 groups each of 15 rats. One group was given tolbutamide suspension (1%) in water containing 0.2% methylcellulose, in a dose of 200 mg/kg. Two other groups were given equivalent doses of tolbutamide, but in presence of 200 mg of kaolin or activated charcoal/kg. The collection of blood, the measurement of blood glucose [1] was carried out as previously described (Said and Saad, 1975). The mean blood glucose levels of each subgroup were compared and differences were tested for significance using Student's *t*-test. The influence of kaolin or activated charcoal on blood glucose level of tolazamide or acetohexamide was carried out similarly.

RESULTS AND DISCUSSION

Data obtained from adsorption experiments fit the linear form of the Langmuir equation:

$$\frac{C}{x/m} = \frac{1}{ab} + \frac{1}{b}C \qquad (1)$$

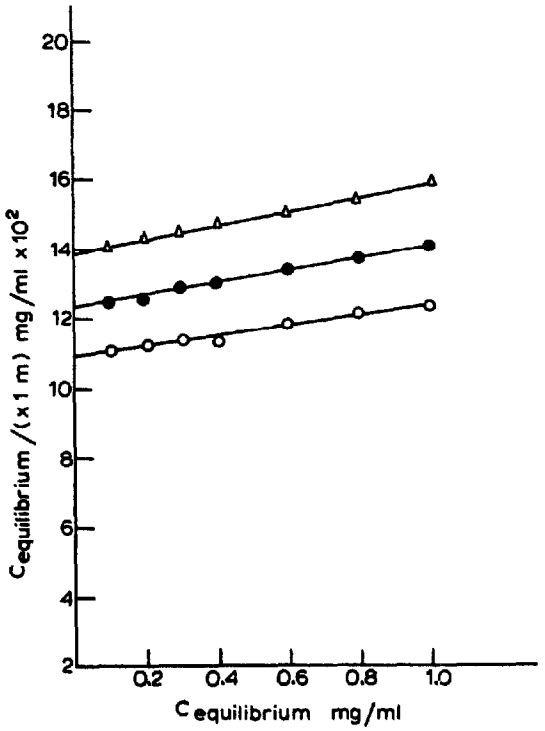
where x/m is the weight of drug in milligrams adsorbed per gram of adsorbent, C is the equilibrium, and a and b are constants. Constant a is related to the force involved in bind-

[1] Eli Lilly, Basingstoke, England.
[2] Upjohn, Kalamazoo, Mich., U.S.A.
[3] Hocchest, Frankfurt, G.F.R.
[4] Ritdei De Haen, Hannover, G.F.R.
[5] B.D.H., Poole, England.
[6] Millipore, Bedford, Mass., U.S.A.
[7] Varian Techtron, UV-VIS, Model 635, U.S.A.

ing the drug to the adsorbent, and constant b is the maximum amount of drug that can be adsorbed per gram of adsorbent. Langmuir isotherms for the adsorption of the drugs to activated charcoal and kaolin appear in Figs. 1 and 2 respectively. From the reciprocal of the slope of each linear curve, the limiting adsorptive capacity of each adsorbent for drugs was calculated (Table 1).

The extent of binding of the 3 drugs by the adsorbent follows this sequence: acetohexamide (653 mg/l kaolin and 692 mg/l charcoal) > tolbutamide (481 mg/g kaolin and 502 mg/g characoal) > tolazamide (456 mg/g kaolin 501 mg/g charcoal).

The 3 oral hypoglycaemics have the same sulphonamide moiety with little difference in side-chains, that varies their polarity. It seems that with the more polar drug (tolazamide), minor adsorption occurs. This is in agreement with Patrick and Eberman (1925), who concluded that for a given solvent, the more soluble solutes are generally less strongly adsorbed than the less soluble ones. Said and Abdullah (1980) have reported similar adsorption of the same 3 drugs on magnesium trisilicate. Moreover, the lipophilic moieties were found to promote drug adsorption to charcoal through hydrophobic interaction with the activated surface of the charcoal particles (Sanvordeker and Dajani, 1975). This explains why a less polar drug like acetohexamide is more adsorbed than tolazamide or tolbutamide.



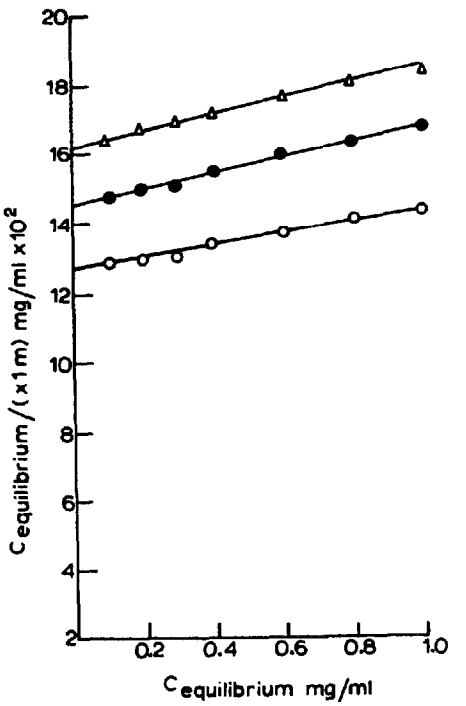


Fig. 1. Langmuir isotherm for the adsorption of acetohexamide, tolazamide and tolbutamide on charcoal at pH 7.4. Symbols: •, tolbutamide; ○, acetohexamide; △, tolazamide.

Fig. 2. Langmuir isotherm for the adsorption of acetohexamide, tolazamide and tolbutamide on kaolin at pH 7.4. Symbols as in Fig. 1.

TABLE 1

ADSORPTIVE CAPACITIES OF ACTIVATED CHARCOAL AND KAOLIN FOR THE DRUGS AT 37°C

Drug	Limiting adsorptive capacity, b [a] (mg/g)	
	Activated charcoal	Kaolin
Acetohexamide	692	653
Tolbutamide	502	481
Tolazamide	501	456

[a] b appears in the Langmuir equation and denotes the theoretical maximum adsorptive capacity of an adsorbent for a particular drug.

Table 2 shows the extent of desorption of acetohexamide, tolazamide and tolbutamide in pH 7.4 phosphate buffer. It seems that the extent of desorption of the 3 drugs is relatively higher from activated charcoal (11–38.8%) than from kaolin (1.8–24.5%). The comparatively higher desorption of drugs from charcoal may illustrate weak physical interaction between the drugs and such an adsorbent, (Sorby, 1965).

Fig. 3 illustrates the effect of activated charcoal and kaolin on the hypoglycaemic activity of acetohexamide, tolazamide and tolbutamide. The mean blood glucose concentration of the 24-h fasted male albino rats was 73.25 ± 2.55 mg/100 ml and is significantly higher than all of the treated groups. As illustrated in Fig. 2, the reduction in blood glucose level was lessened in the systems containing either kaolin or activated charcoal. The difference between blood glucose concentrations of control rats given drugs alone on the one hand and the corresponding values of those and animals given drugs with either activated charcoal or kaolin were found to be statistically significant (Student's t-test $P = 0.01$ level [8]). At 2 h the mean blood glucose level of rats given tolbutamide alone is 2.5 mg/100 ml, whereas it is up to 19.1 and 30.01 mg/100 ml in presence of activated charcoal and kaolin respectively. Moreover, the mean blood glucose level of rats given acetohexamide at 2 h is 22.5 mg/100 ml and this increases to 39.1 and 50 mg/100 ml in presence of activated charcoal and kaolin respectively. Furthermore, at 2 h the mean blood glucose level of rats given tolazamide is 6.5 mg/100 ml, but is 25.2 and 35.01 mg/100 ml in presence of activated charcoal and kaolin respectively. These data emphasize a decreased absorption of the 3 oral hypoglycaemics in the presence of the tested adsorbents. Thus, it seems that both activated charcoal and kaolin alter the extent of absorption of the tested oral hypoglycaemics primarily by the virtue of the fact that they probably limit the amount of the drug available at the site of absorption. It is worth noting, that the relatively higher blood glucose values in the presence of kaolin indicate a much decreased absorption. Significant differences ($P = 0.05$ level) were found between the blood glucose level at the 2 h for rats given drugs with activated charcoal and those given drugs in the presence of kaolin. This may be due to the relatively higher desorption of drugs from charcoal.

[8] At 1, 2 and 3 h.

TABLE 2

PERCENTAGE OF DESORBED DRUG USING PHOSPHATE BUFFER pH 7.4 AT 37°C

Drug	Activated charcoal [a]	Kaolin [a]
Acetohexamide	11.3–18.3	1.8–3.2
Tolbutamide	29–37.5	19–20.2
Tolazamide	35.5–38.8	22.8–24.5

[a] Values are the range of per cent drug desorbed, using the different adsorbent residues left after adsorption experiments.

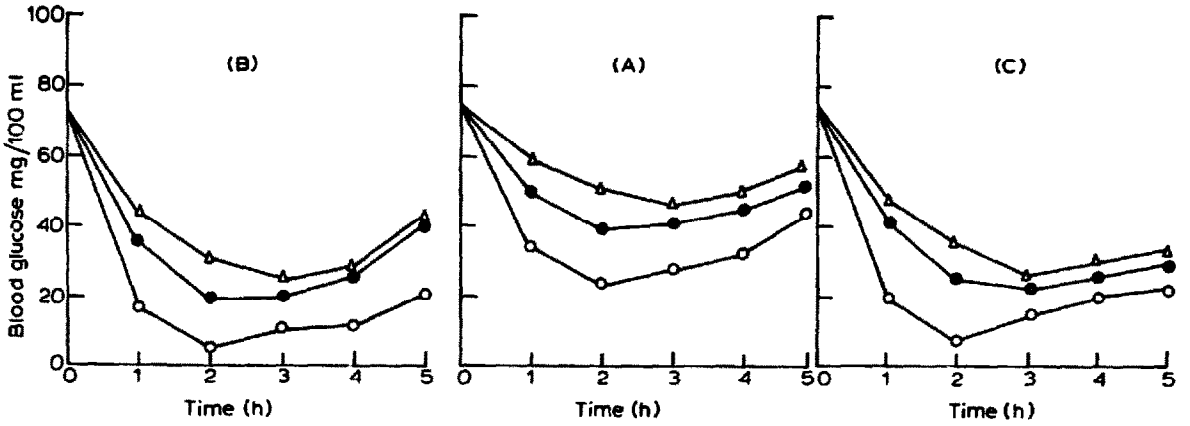


Fig. 3. Effect of activated charcoal and kaolin on the hypoglycaemic activity of acetohexamide (A) tolbutamide (B) and tolazamide (C). Symbols: ○, drug alone; and ● and △, in presence of activated charcoal and kaolin respectively.

The clinical implications of adsorption of the 3 oral hypoglycaemics by activated charcoal are obvious in the cases of co-administration of charcoal with the drugs or the use of activated charcoal as antidote. Also, the possibility of interfering with the bioavailability of these oral hypoglycaemics by co-administration with kaolin-containing suspensions must be considered.

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