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ANTIDOTAL PROPERTIES OF ACTIVATED CHARCOAL*

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The capacity of charcoal to bind poisonous agents can be determined in vitro by means of Langmuir's adsorption isotherm. The method is a suitable means for studying the influence of various parameters, e. g. pH, or concurrence with other concomitant material on the binding capacity. The saturation value of the isotherms of chemical agents is very often referred to as an index of the antidotal value of the adsorbent. However, this physical constant is by no means representative of the in vivo conditions and does not necessarily reflect the therapeutic efficacy of the antidote, because a number of physiological parameters compete with the binding. The only reliable test is animal experimentation where the sample of activated charcoal is administered concomitantly with – or preferably following – installation of the poisonous drug into the stomach, and the rate of absorption of the drug into the circulation and/or the influence on mortality is evaluated. A series of highly discrepant results obtained in in vitro and in vivo tests are presented. Activated charcoal should be used without any other chemical. Combinations with other neutralizing antidotes, such as tannic acid or magnesium oxide (e. g. in the form of the so-called »universal antidote«) are more or less ineffective on account of mutual inactivation of the ingredients.

The idea of the antidotal use of charcoal originates from its technical application. As an adsorbent, it is known since the 15th century. It was used for the removal of unwanted coloured material in solutions, e. g. for the discoloration of sugar syrup in the commercial sugar production. The first report on the antidotal use of charcoal seems to be that of the French physician *Bertrand* in 1813 (1), who self-experimented with arsenic. Thereafter, the drug was recommended several times with or without convincing evidence of its beneficial action. It was not until 1880 when *Ostwald* and, later on, *Freundlich* (1906) and *Langmuir* (1916) described the physics of adsorption which enabled pharmacologists

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to understand the reaction as obeying the law of mass action. *Wiechowski*, pharmacologist in Prague, was the first to do systematic studies on the antidotal properties of activated charcoal. He described (2) the binding of methylene blue as a test procedure for determining the activity of a preparation. His work initiated a widespread use of charcoal on the continent. This deserves mention because activated charcoal in these days seems to have been rediscovered in the USA (3). In England and USA, meanwhile, a combination of charcoal with tannic acid and magnesium oxide was propagated as a »universal antidote« (4). Some time ago, we performed some studies on the binding capacity of this so called universal antidote, and of charcoal alone (5). On this occasion, some factors which influence the binding of drugs to charcoal were investigated more extensively.

The binding of chemicals to an adsorbent is characterized according to *Langmuir*, by an adsorption isotherm, for example with phenobarbital (Fig. 1). This curve demonstrates that the amount of bound drug is a

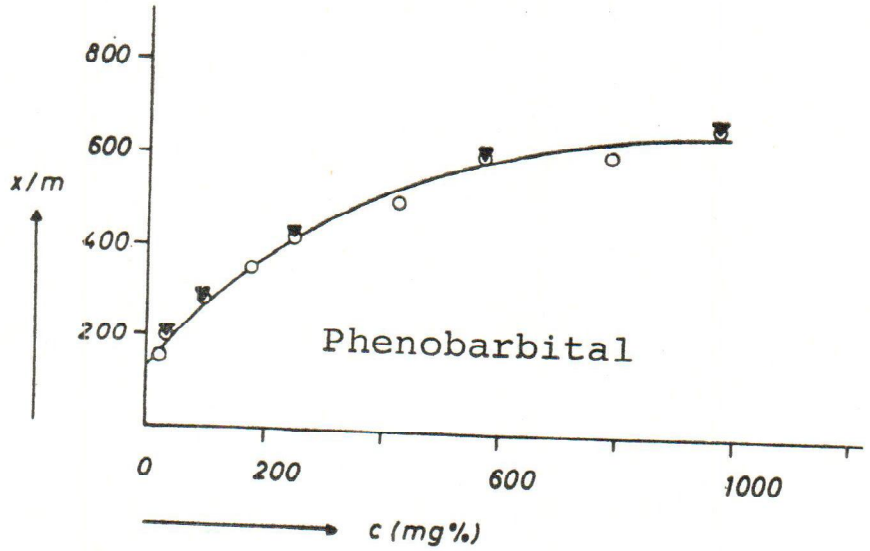

Fig. 1. *Binding of phenobarbital to activated charcoal. – x/m = mg of phenobarbital bound per gm of charcoal; c (mg%) = concentration of phenobarbital not adsorbed*

function of its actual concentration. The asymptotic approach of the curve reveals that some of the drug remains in the free (unbound) state. If a mixture of drug and charcoal passes through the intestinal tract, the free part of the drug is due to adsorption through the intestinal wall. Consequently, the equilibrium of drug and charcoal is reestablished according to the law of mass action, and a desorption of drug from charcoal takes place. Thus, a considerable portion of the ingested drug may get into

the circulation, in spite of a »high binding capacity of charcoal«. This makes clear that the most frequently used formula for the binding capacity: per cent of drug bound by a certain amount of charcoal, is not a satisfactory means for characterizing the detoxifying potency of the antidote.

Several parameters may influence the binding of drugs in vivo:

1) the velocity of gastrointestinal passage

2) the speed and degree of absorption of the (unbound) drug through the wall of the gastrointestinal tract

3) the actual concentrations of drug and adsorbent

4) the kind and amount of intestinal ingredients, containing substances which may interfere with the binding of the drug to be detoxified, and

5) the pH in the stomach and small intestine.

Of these, the only physical parameter of importance, pH, has been studied in some of our recent experiments with a number of alcaloids. The results are demonstrated in some graphs. A great and, most probably decisive, variation of binding with pH is seen with nicotine (Fig. 2), the binding in alkaline pH amounting to more than tenfold compared to that in acid solution, as found with gastric juice. Smaller variation is found with atropine and quinine, and it is only negligible (Fig. 3) with strychnine and yohimbine. It is generally accepted that, with basic compounds like alcaloids, the binding increases with pH. However, in some cases the reverse holds true, as is shown (Fig. 4) with the alcaloids aconitine and veratrine. In general, there is no clear relationship between the variation of binding with pH and the pKa-values of the compounds. In some cases, however, pH and the duration of the presence of a drug plus charcoal in the stomach may be of high importance.

The biological parameters influencing drug adsorption by charcoal are not open to clear survey or prediction. This implies that physical tests in general cannot serve as reliable assay methods for detoxification. The only satisfactory way to determine detoxification quantitatively is the biotest in the intact animal. In such a test method, the conditions of poisoning in humans should be simulated as closely as possible. So the antidote should be applied *after* the poisonous drug. One way to evaluate the antidotal value is to determine the amount of drug absorbed into the circulation. The applicable doses of poisons are then limited to sublethal, or by some authors even to subtoxic, levels. However, the main aim of the treatment of acute poisoning is to save life. Consequently, a better experimental criterion is the comparison of lethality in groups of animals likewise poisoned, but differently treated. I think that this is worth emphasizing because only recently some groups of investigators have given preference to determining drug blood levels. The reason why quite different results are obtained with the two methods,

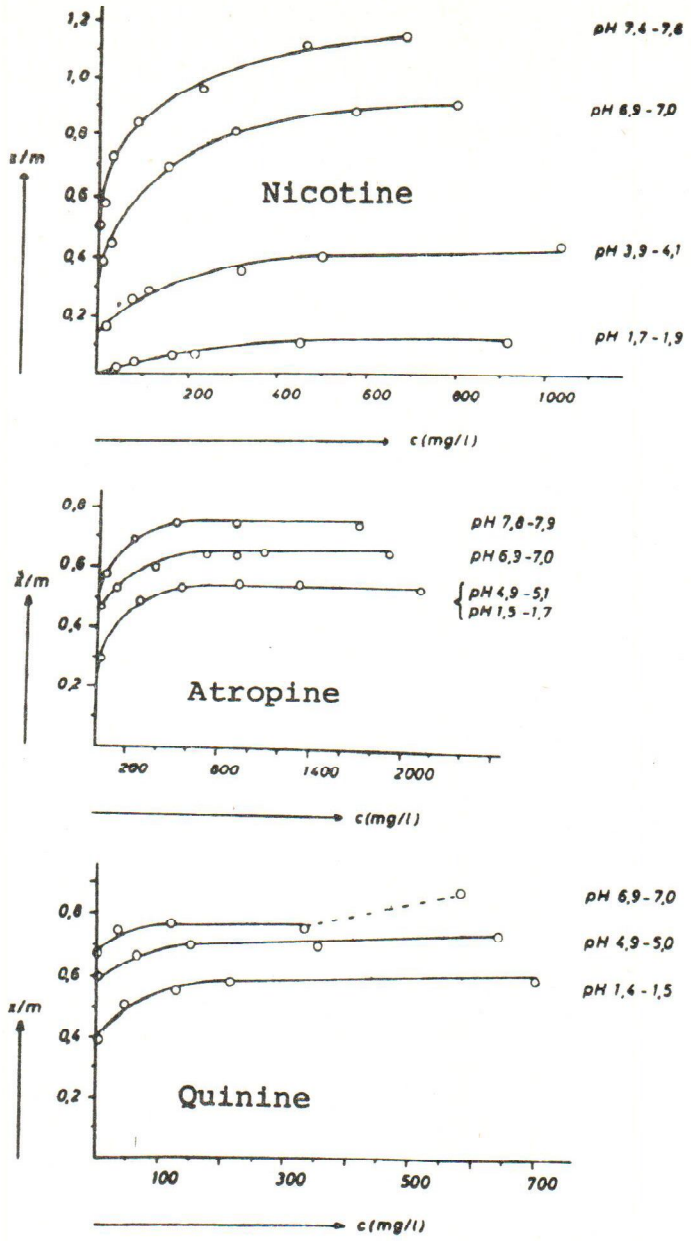

Fig. 2. *Binding of nicotine, atropine, and quinine to activated charcoal at different pH*

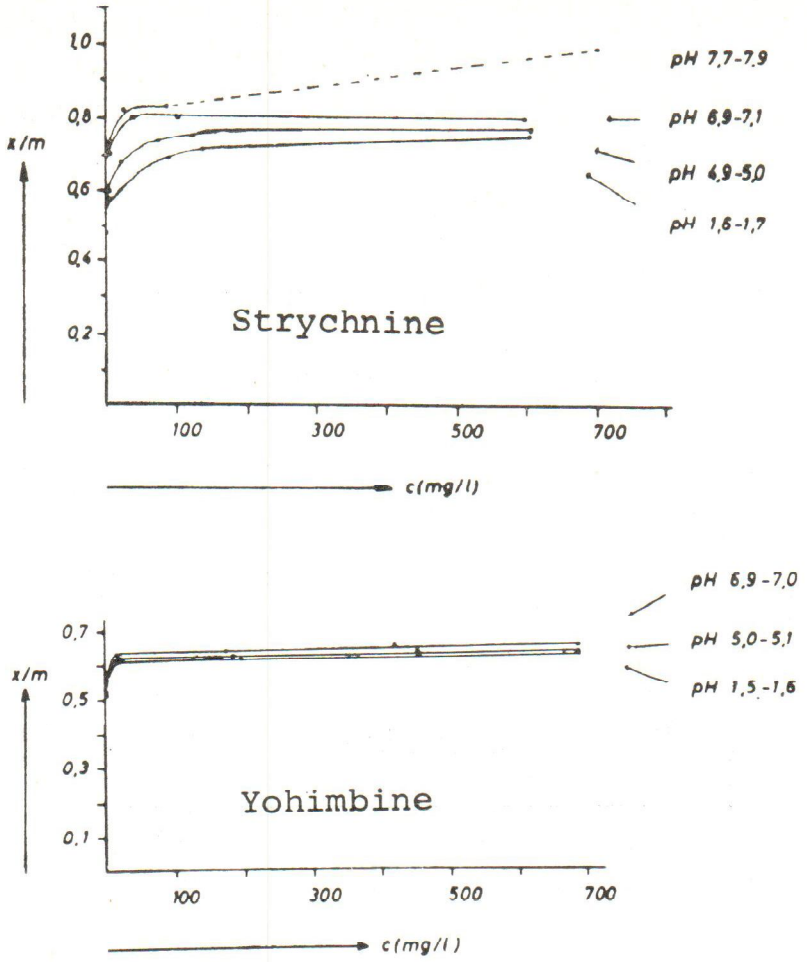

Fig. 3. *Binding of strychnine and yohimbine to activated charcoal at different pH*

especially better detoxification figures with the determination of blood levels, is clearly demonstrated by a glance at the shape of *Langmuir's* adsorption isotherm: the binding of the drug is far more efficient with low than with high concentrations. So the best criterion of the antidotal value of charcoal is determination of the LD_{50}-values of a poison with and without treatment with charcoal.

The shape of the isotherm deserves further consideration (Fig. 5). As the actual concentration of both the poisonous agent and the antidote varies in different parts of the gastrointestinal tract at different periods, the bound portion of the drug depends not only on the value of satura-

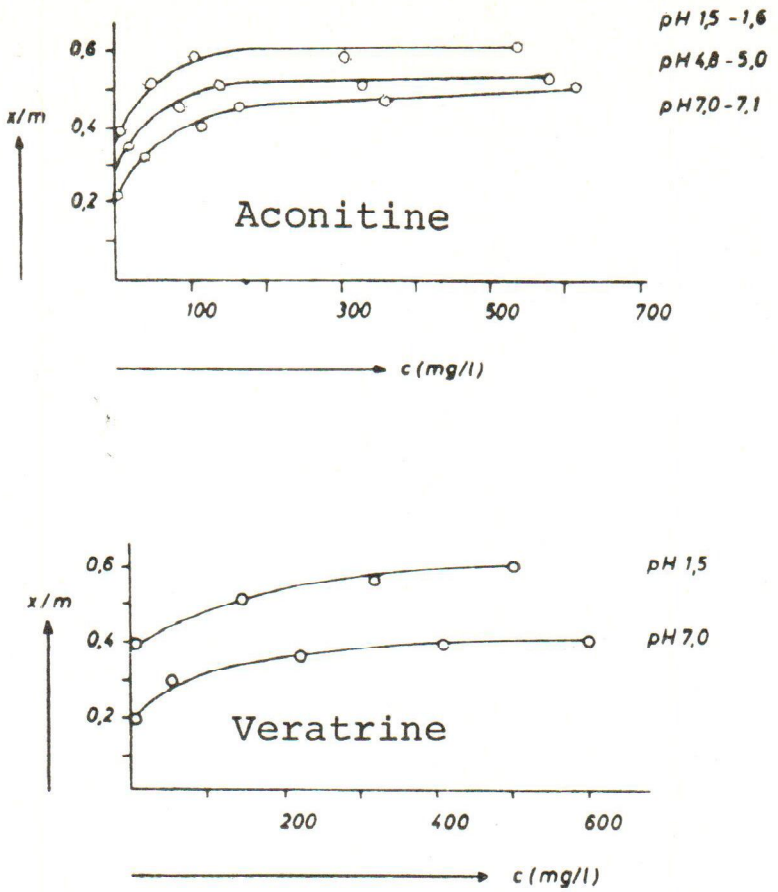

Fig. 4. *Binding of aconitine and veratrine to activated charcoal at different pH*

tion but also on the slope of the curve: the steeper the inclination, the better the binding at lower concentrations, irrespective of the total binding capacity. We have tested the validity of this physically derived hypothesis by mortality tests in mice with a series of alcaloids and phenobarbital. A comparison between the adsorption isotherms and the quotient of LD_{50}-values with and without the application of charcoal reveals no satisfactory correlation, indicating once more that at present there is no reliable physical test for predicting the real therapeutic value of activated charcoal.

Finally, it should be emphasized that charcoal must not be combined with other potential antidotal material. In most American textbooks of toxicology such a mixture is mentioned in the form of the so called »universal antidote«. We demonstrated in experiments on mice (5) that

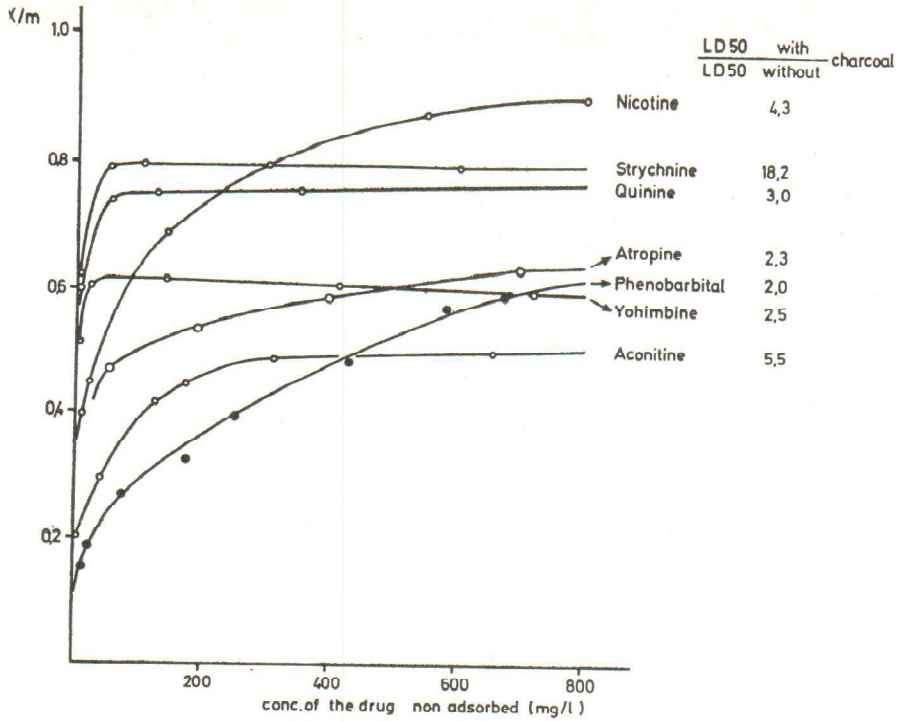

Fig. 5. *Adsorption isotherms of various poisonous agents, and detoxification index after administration via the oral route as determined by the LD_{50} in mice*

this combination provides – if any – only minimal protection as compared with charcoal which is by far a superior agent. The ineffectiveness of »universal antidote« is due to interreactions of the three components charcoal, tannic acid and magnesium oxide, resulting in mutual inactivation and loss of the antidotal properties which each ingredient possesses per se. Consequently, charcoal should be administered only without other intestinal antidotes.

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Sažetak

ANTIDOTSKA SVOJSTVA AKTIVNOG DRVENOG UGLJA

Sposobnost drvenog uglja da veže otrovne supstancije može se odrediti in vitro pomoću Langmuirove adsorpcione izoterme. Ova je metoda prikladna za proučavanje utjecaja raznih parametara kao što su pH ili prisutnost drugih supstancija na sposobnost vezanja. Vrijednost zasićenja izoterma kemijskih supstancija vrlo se često smatra indeksom antidotske vrijednosti adsorpcijskog spoja. Međutim, ta fizikalna konstanta ni u kom slučaju ne reprezentira in vivo uvjete i nužno ne odražava terapijsku efikasnost antidota jer više fizioloških parametara sudjeluje kod vezanja. Jedini pouzdani test su eksperimenti sa životinjama kad se uzorak aktivnog drvenog uglja daje istovremeno ili po mogućnosti nakon aplikacije otrova u želudac i određuje brzina apsorpcije otrova u cirkulaciju i/ili utjecaj na smrtnost. Prikazan je niz vrlo protivurječnih rezultata dobivenih in vitro i in vivo pokusima. Aktivni drveni ugalj mora se primijeniti bez ijedne druge kemijske supstancije. Kombinacije s drugim neutralizirajućim antidotima, kao što su taninska kiselina ili magnezijev oksid (npr. u obliku tzv. »univerzalnog antidota«), manje ili više su neefikasne zbog uzajamne inaktivacije sastojaka.

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