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BRIEF COMMUNICATION

Potential Pharmacodynamic Effect of Charcoal on Theophylline Neurotoxicity in Normal Rats

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HOFFMAN, A. *Potential pharmacodynamic effect of charcoal on theophylline neurotoxicity in normal rats.* PHARMACOL BIOCHEM BEHAV 43(2) 621–623, 1992.—Previously, it has been found that repeated oral administration of activated charcoal (AC) to rats with renal failure markedly decreased the sensitivity of the CNS to the neurotoxic-convulsant effect of theophylline. The present study was designed to investigate whether this effect also occurs in normal rats. Normal rats received AC per os in either a single dose or in six doses every 8 h. Control animals received equal volumes of water. Two hours following the last AC dose, animals were infused IV with theophylline until the onset of maximal seizures. Although rats pretreated with repeated administrations of activated charcoal required a larger total theophylline dose to induce convulsions, the theophylline concentrations in the serum and brain at the onset of the neurotoxic episode were not affected by the charcoal pretreatment. It is, therefore, concluded that the gastrointestinal dialysis produced by the activated charcoal had no apparent effect on theophylline-induced neurotoxicity in normal rats.

Theophylline Neurotoxicity Activated charcoal Pharmacodynamics Induced seizures Gastrointestinal dialysis

ORAL administration of activated charcoal (AC) is a well-known clinical detoxification procedure used in the treatment of overdosed and poisoned patients (2,4,16,18). Activated charcoal, by producing an "infinite sink" condition in the gut lumen, enhances the passive diffusion of various xenobiotics and endogenous compounds from the systemic circulation into the gut lumen, a process that has been called "gastrointestinal dialysis" (9). In addition, AC can prevent the recycling of certain molecules between the systemic circulation and the gastrointestinal (GI) tract and, consequently, change their concentration in biological fluids (8). The potency of AC in reducing the serum concentration of certain endogenous compounds has been verified. This includes the reduction of various uremic toxins (5,12), porphyrin (13) and bilirubin (1). Several of these compounds are involved (directly or indirectly) in the regulation of different physiological, biochemical, and pharmacological processes. Thereby, the removal of such endogenous molecules may affect the body's homeostasis as well as many other biologic functions, including the response to drugs. There are clear indications that various endogenous compounds that affect CNS function, such as several of the low-molecular-weight benzodiazepine receptor ligands (20) and δ-sleep-inducing peptide (17), are present in the systemic blood circulation. Removal of a CNS-active endogenous component by dialysis may likely affect the pharmacodynamics (concentration–pharmacological effect relationship) of neuroactive medications.

Until now, the antidotal efficacy of AC, as well as other orally administered sorbents, has been attributed solely to its ability to affect pharmacokinetic parameters (i.e., drug concentration vs. time profile) of the toxic drug. These include reduced absorption, changes in serum protein binding with consequent changes in the volume of distribution, and enhanced elimination. However, the potential pharmacodynamic effect(s) of AC has so far been neglected.

In a previous study, we have shown that AC administered orally to rats with acute renal failure necessitated a large increase in the dose and concentrations of theophylline required to produce maximal seizures compared to the result observed in untreated uremic rats (6). This was a reversal of the greater

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sensitivity of the CNS to the neurotoxic (convulsive) action of theophylline found in rats with acute renal failure than found in normal animals (15).

This result clearly demonstrated that AC may have an as yet unidentified role in the treatment of drug toxicity, namely, by reducing the body's sensitivity to neurotoxic effects. Therefore, the objective of the present study was to examine whether AC administrated orally affects the pharmacodynamics of theophylline neurotoxicity in normal rats, as it did in uremic rats and, consequently, help enhance our understanding of the mechanism(s) by which AC decreases the CNS's sensitivity to the theophylline-induced convulsive effect in uremic rats.

METHOD

Male Sabra rats (weighing 170–250 g), obtained from the Animal Breeding Center of the Hebrew University (Jerusalem, Israel) and maintained on a laboratory animal diet (Amrod #931, Ambar Food Mills, Israel), were used in this investigation. An in-dwelling cannula was inserted into the rat's right jugular vein (19), under light ether anesthesia, and animals were then housed individually in metal cages with food and water available ad lib.

Using different schedules of charcoal administration, the effects of AC on theophylline neurotoxicity were investigated in two experiments. In the first study, each rat received a single dose of 200 mg AC (SuperChar, Gulf Bio-Systems Inc., Dallas, TX) in water (total 1 ml) 2 h prior to the experiment; this dose is equivalent to the dose (1 g/kg) of charcoal used as adsorbent in adult humans and children. In the second study, for 48 h following surgery each rat received 200 mg AC every 8 h for a total of six doses, with the last dose given 2 h prior to the experiment. Charcoal was administered by stomach tube under light ether anesthesia. In both experiments, control rats received only water according to the same schedule. The theophylline neurotoxicity experiments were carried out as previously described (14). Rats were infused IV with theophylline (as aminophylline, 100 mg/ml distilled water) at a rate of 1.03 mg theophylline/min until the onset of maximal seizures, as evidenced by forelimb flexion and, usually, tonic hindlimb extension. At that time, both blood (for serum) and brain were obtained and stored in a freezer pending assay. Concentrations of theophylline in serum and one hemisphere of the brain were determined by high-performance liquid chromatography (HPLC) following extraction with organic solvent consisting of 5% propanolol in chloroform, with β-hydroxypropyltheophylline (Sigma Chemical Co., St. Louis, MO) as internal standard. These procedures have already been described in detail (14). The data were analyzed statistically by the Mann-Whitney *U*-test.

RESULTS AND DISCUSSION

Theophylline is a bronchodilator that is widely used for the treatment of reversible obstructive airway disease. Its effect on pulmonary function is concentration dependent. When theophylline-therapeutic plasma concentrations are exceeded, adverse cardiovascular and CNS results occur probably due to the adenosine antagonistic effect of theophylline at the A_1- and A_2-purinoreceptors (11). One of the most serious of these adverse effects is generalized seizures, which are frequently followed by permanent neurological damage or death. Oral administration of AC is known to be an effective treatment for theophylline toxicity.

TABLE 1

EFFECT OF A SINGLE DOSE OF ORALLY ADMINISTERED AC ON THEOPHYLLINE CONCENTRATIONS AT THE ONSET OF MAXIMAL SEIZURES IN RATS INFUSED WITH THEOPHYLLINE*

Variable	Rats Pretreated With Activated Charcoal	Control Rats
Total dose (mg/kg)	291 ± 24	283 ± 15
Serum concentration (μg/ml)	410 ± 34	405 ± 32
Brain concentration (μg/mg)	242 ± 23	236 ± 30

*Results are reported as mean ± SD (n = 9). Theophylline was infused IV 2 h following oral administration of 200 mg activated charcoal aqueous suspension or water.

It has been customary to evaluate the toxicity of drugs according to the dose required to produce a toxic episode (e.g., LD_{50}). The impact of the sorbent antidotal effect on drug toxicity is evidenced by an increased dose required to produce equivalent toxicity. However, because the dose required to induce the toxic effect is a function of both the drug's pharmacokinetic performance, as evidenced by the toxic drug concentration in biologic fluids following a given dose, and the intensity of the toxic effect induced by these concentrations (i.e., concentration-response relationship), the mechanism(s) by which the sorbent agent reduces toxicity cannot be clearly determined. The end result could be due not only to an enhanced clearance but also from reduced CNS sensitivity. Therefore, the increase in the total dose required to induce generalized seizures in sorbent-treated animals, found in this study (Table 2), could result from pharmacokinetic actions of AC, as well as pharmacodynamic mechanisms, as was found in the case of uremic rats treated with AC (6). While much is known about the mechanism of the pharmacokinetic effects of AC in enhancing the total body clearance of many drugs, including theophylline by GI dialysis (3,10), the potential effects of AC on the pharmacodynamics of other drugs have not yet been reported in the literature.

In this experiment, the data clearly show that in normal rats, oral administration of AC did not attenuate the CNS's sensitivity to theophylline-induced neurotoxicity. Neither a single dose nor six consecutive doses over 48 h had any apparent effect on serum and brain theophylline concentrations at the onset of maximal convulsions (Tables 1 and 2). However, as opposed to pretreatment with only a single dose of AC

TABLE 2

EFFECT OF REPEATED ORAL ADMINISTRATION OF AC ON THEOPHYLLINE CONCENTRATIONS AT THE ONSET OF MAXIMAL SEIZURES IN RATS INFUSED WITH THEOPHYLLINE*

Variable	Rats Pretreated With Activated Charcoal	Control Rats
Total dose (mg/kg)	352 ± 97*	283 ± 42
Serum concentration (μg/ml)	418 ± 44	402 ± 28
Brain concentration (μg/mg)	252 ± 37	240 ± 38

Results are reported as mean ± SD (n = 12). Rats received 200 mg activated charcoal in water or only water by gavage every 8 h for six doses. Theophylline was infused IV 2 h following the last dose.
*Significantly different from control group ($p < 0.04$).

pretreatment with AC for 2 days prior to the experiment necessitated a statistically significant increase in the total theophylline dose required to produce maximal seizures in normal rats.

The increased total theophylline dose required to induce maximal seizures following pretreatment with six doses of AC may have been due to the ability of AC to elevate total body clearance of theophylline (3,10). However, as evidenced by visual examination following dissection of the cadavers, a single dose of AC administered 2 h before the study was not sufficient to increase theophylline clearance by gastrointestinal dialysis. In the group of animals pretreated with only a single dose of AC administered prior to the experiment, the AC did not distribute throughout the GI tract and was mainly located in the stomach. On the other hand, following 48 h of pretreatment with AC the distinguishing marks of the charcoal were observed throughout the GI tract.

The differences between the results of this investigation carried out in normal rats and the pronounced effectiveness of orally administered AC in decreasing the sensitivity of rats with renal failure to theophylline neurotoxicity (6) are interesting. It could be that in rats with renal failure AC is associated with the removal of an endogenous substance(s) that accumulates in the rat but is not present in effective concentrations in normal rats.

A recent study (7) showed that IV administration of concentrated dialysate of serum from rats with renal failure to normal rats did not affect the CNS's sensitivity to theophylline-induced neurotoxicity. The results of that study, together with the above outlined study, support the possibility that the responsible component(s) in uremic blood are rapidly eliminated in normal rats. These substance(s) probably affect the purinoceptors in the CNS that are known to be involved in the convulsive effect induced by an overdose of theophylline.

Despite the negative findings of this study, considering the potency of GI dialysis to change the rate of elimination of endogenous substances, and thereby their concentration in body fluids, it appears advisable to extend this investigation to other selected drugs and toxic agents, especially in disease states in which endogenous components tend to accumulate in the body.

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