BINDING OF SELECTED TOXICANTS TO ACTIVATED CHARCOAL

by

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THE IN VITRO ADSORPTIVE AFFINITY OF BARBITAL, ETHYLENE GLYCOL AND SODIUM FLUORIDE FOR ACTIVATED CHARCOAL

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The In Vitro Adsorptive Affinity of Barbital, Ethylene Glycol and Sodium Fluoride for Activated Charcoal. ADAUDI, A. O. AND OEHME, F. W. (197_). Toxicol. Appl. Pharmacol. 00,00-00. The in vitro adsorption by activated charcoal (AC) of barbital, ethylene glycol (EG) or sodium fluoride (NaF) was determined by adding quantities of each chemical to freshly drawn heparinized canine blood. Activated charcoal, at 4 times the amount of chemical used, was added to each mixture and incubated at 37°C. The concentration of unbound chemical was determined before and at 15 min intervals for 3 hr after AC addition. Standard solutions of the same toxicants in citrated ovine blood were circulated through commercially prepared AC cartridges (ACC) and sequential concentrations of free drug were similarly determined. The AC and ACC, respectively, adsorbed 45.9% and 100% of the original concentrations of barbital and 19.5% and 34.3% of the EG, but only 4.2% and 0.8% of the NaF originally present in the blood was removed.

Activated charcoal (AC) has a broad spectrum of adsorption for various toxicants (Corby et al., 1970; Corby and Decker, 1974; Hayden and Comstock, 1974; Holt and Holz, 1963). In vitro and in vivo observations of the adsorptive capacity of AC have prompted many to advocate AC for the treatment of exogenous poisonings for which there are no antidotes (Belz, 1974; Belz and Bader, 1974; Chin et al., 1970; Comstock, 1971; Corby and Decker, 1968; Crammer and Davies, 1972; Decker et al., 1968a, b; Dordoni and Wilson, 1973; Fane and Decker, 1970; Ferguson, 1970; Furr and Carson, 1975; Gazzard et al., 1974; Hartel et al., 1973; Levy and Gwilt, 1972; Levy and Tsuchiya, 1972; Lipscomb and Widdop, 1975; Matthew, 1972; Phansalkar and Holt, 1968; Sparks et al., 1971; Tsuchiya and Levy, 1972a, b) rather than attempting the hazardous and sometimes unreliable application of emetics and gastric lavage (Decker, 1971; Fane et al., 1971). Recent in vitro studies do not support the earlier belief that AC is a universal adsorbent (Picchioni, 1970), and there are no clear criteria to predict which toxicants will be effectively or extensively adsorbed by AC.

The current treatments for barbital and sodium fluoride are mainly supportive and symptomatic (Abukurah et al., 1972; Berman et al., 1973; Lawson and Proudfoot, 1971; Mann and Sandberg, 1970; Yolken et al., 1976), although some have stamped barbiturate supportive therapy as "therapeutic nihilism" (Koppanyi and Fazekas, 1950; Koppanyi and Fezekas, 1952). Others have suggested AC for the therapy of acute barbiturate poisoning (Chin et al., 1970, Corby et al., 1970; Fane and Decker, 1970; Mann and Sandberg, 1970; Matthew, 1975; Rosenbaum, 1972; Yatzidis, 1965; Yatzidis, 1971). Current management of ethylene glycol toxicosis includes the use of ethanol and sodium bicarbonate, but treatment is only effective when initiated at

an early stage of poisoning (Penumarthy and Oehme, 1975; Sanyer et al., 1973). Since most patients are presented at a later stage of intoxication, effective methods for the removal of circulating toxicants and their metabolites are vital to the patients' survival. The use of activated charcoal hemoperfusion offers sufficient promise in this direction to warrant further evaluation.

These studies were conducted to determine the in vitro binding capacity of AC powder and a commercially prepared AC cartridge (ACC) for barbital, ethylene glycol and sodium fluoride. The potential use of AC in a hemoperfusion system to accelerate the removal of these toxicants from the blood of acutely poisoned patients was thereby evaluated.

METHODS

Studies with Activated Charcoal Powder

Mixtures of freshly drawn heparinized canine blood were prepared containing 0.25 mg barbital[1]/ml, 11.13 mg ethylene glycol[1] (EG)/ml, or 22 mg sodium fluoride[2] (NaF)/ml. Blood volumes of 20 to 100 ml were used. Activated charcoal[3] (20 x 50 mesh, coconut base) was added to each blood-chemical mixture at four times the amount of toxicant present. The amounts of AC used were 20 mg for the barbital mixtures, 45 mg for EG, and 200 mg for the NaF mixtures. The mixtures were maintained in a waterbath at 37°C. Chemical concentrations were determined before and after addition of the AC. One ml of toxicant-blood mixture for barbital and EG, or 5 ml of the mixture for NaF, was taken for analysis at 15 min intervals for 3 hr.

Studies with Activated Charcoal Cartridge

Mixtures of citrated ovine blood containing 150 mg barbital/l,

579 mg EG/l or 500 mg NaF/l were prepared and circulated through a closed ACC hemoperfusion system at the rate of 150 ml blood/min. The hemoperfusion system consisted of a pump,[4] pressure monitor,[4] ACC[4] and a blood tubing set[5] (Fig. 1). The ACC contained approximately 100 g of AC, and was prepared wet with 300 ml of solution containing 0.9% sodium chloride and 0.25% glucose. One or 5 ml of whole blood was collected from the system for quantification at 15 min intervals for 3 hr.

Assay Procedures

Barbital. Barbital was determined in 1 ml of whole blood by a modified method of Goldbaum (1952); 5 ml of approximately 0.45N sodium hydroxide were used to extract the barbital from the chloroform aliquot. The barbital standard curve obeyed Beer's Law for concentration from 2 to 30 ug barbital/ml of blood. The limit of detection was 1 ug barbital/ml. These findings agree with those of Goldbaum (1952) and Kyle et al. (1953). The mean recovery of barbital from whole blood was 81.3% ± 10.3 (SE).

Ethylene glycol. The EG levels in whole blood were determined by spectrophotometer at 555 nm as described by Harger and Forney (1959). The standard curve for EG in deionized water did not obey Beer's Law as concentrations above 300 ul EG/l caused a disproportionately greater absorbance, as was also observed earlier by Harger and Forney (1959). The limit of sensitivity was 72 ug EG/ml, and the mean recovery from whole blood at 300 ul EG/l was 73.7% ± 4.0. At a concentration of 700 ul EG/l the mean recovery was 83.3% ± 3.5.

Sodium fluoride. Five ml of whole blood was centrifuged and 1 ml of plasma added to 50 ml deionized water. The fluoride level in the 51 ml

mixture was determined by ion specific electrode (Orion, 1975). The limit of sensitivity was 1 ug NaF/ml plasma. The mean recovery of NaF from whole blood was 99.1% ± 0.2 at 100 ug NaF/ml and 103.0% ± 0.4 at a concentration of 1 ug NaF/ml.

RESULTS

The analytical results for AC and ACC are given for barbital in Table 1, for EG in Table 2, and for NaF in Table 3.

At the end of 3 hr, 2.0 mg of the barbital originally present in the blood had been adsorbed by the 20 mg AC powder (Table 1); thus the AC adsorbed the barbital equivalent of 10.0% its own weight. When the barbital was circulated through the ACC, the barbital level decreased below the detectable limit within 45 minutes (100% adsorption).

The 45 mg of AC powder adsorbed 2.0 mg of EG; this was equivalent to 4.4% of the AC weight (Table 2). The approximately 100 g ACC adsorbed 196.7 mg EG (34.3% of the original total blood EG).

The 0.1 mg of NaF adsorbed by the 200 mg of AC powder was equivalent to 0.05% the weight of the AC used (Table 3). Only 4.0 mg of NaF (0.85% the original amount of NaF present) was adsorbed by the ACC.

In the AC studies with all 3 chemicals, and in the ACC experiment using EG and NaF, maximum adsorption by the charcoal occurred rapidly and in most cases within the first 15 minutes. The overall adsorption of barbital by AC and ACC was very good; it was moderate for EG and poor for NaF (Figs. 2, 3). However, the affinity of the ACC for barbital gradually decreased (Table 1), but total adsorption of barbital was still completed within 45 minutes.

DISCUSSION

The adsorptive capacity of various brands of AC may differ as much as fifty-fold (Holt and Holz, 1963). The adsorptive capacity of any particular brand of AC varies not only with the specific chemical structure of the foreign compound, but also with the milieu in which the drug is found (Hayden and Comstock, 1975). Chin et al. (1970) found that 30 mg of AC adsorbed 3.76 mg of pentobarbital at pH 1.5 (12.57% of its weight) and 2.92 mg of pH 8.5 (9.77% of the AC weight) in simulated gastric fluid. Picchioni et al. (1974) observed that 300 mg of AC adsorbed 3.2% of its own weight as pentobarbital.

The adsorptive capacity of AC for barbital is reportedly about double that for pentobarbital (Holt and Holz, 1963; Hayden and Comstock, 1975). The 10% adsorptive efficacy of AC for barbital thus compares favorably with the results obtained by Chin et al. (1970) and Picchioni et al. (1974).

The 2 mg of EG adsorbed by 45 mg of AC was the same amount of barbital adsorbed by only 20 mg of AC. The affinity of AC for barbital was more than twice its affinity for EG. The maximum amounts of ethyl alcohol, a structural analogue of EG, adsorbed by 100 g of AC were 30 g and 51 g, while the same amount of AC adsorbed 70 g of barbital (Hayden and Comstock, 1975).

The poor adsorptivity observed of NaF by AC supports the statement by Decker et al. (1968b) that, although the adsorptivity of AC does not seem to be correlated with chemical structures, highly ionic substances of low molecular weights are poorly adsorbed.

The complete removal of the 145 mg barbital from the blood by the ACC hemoperfusion system is compatable with previous work in which all the

barbiturate in plasma was removed with a flow rate of 250 ml/min during one pass through ACC (Dedrick et al., 1967; DeMyttenaere et al., 1967; DeMyttenaere et al., 1968; Dunea and Kolff, 1965; Hagstam et al., 1966; Yatzidis, 1971).

In addition to the moderate affinity of EG for AC and the poor affinity of NaF to AC, the adsorption of these chemicals to the ACC was rapid and the point of apparent ACC saturation quickly attained (Fig. 3). The poor adsorptivity of certain compounds has been attributed to a vague "poisoning" effect of the toxicant on the AC (Holt and Holz, 1963).

The described studies has served to examine ACC hemoperfusion therapy for patients poisoned by barbital, EG or NaF. However, the most reliable evaluation of such a technique can best be obtained by in vivo experiments with experimentally poisoned animals.

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[2]Mallinckrodt Chemical Works, St. Louis, Mo.

[3]Pittsburgh Activated Carbon, Calgon Corporation, Pittsburgh, Pa.

[4]Becton, Dickinson and Co. Research, Research Triangle Park, N. C.

[5]Cobe Hemmaflo, Cobe Laboratories Inc., Lakewood, Co.

TABLE 1

BARBITAL IN WHOLE BLOOD (WB) BEFORE AND AFTER ADDITION OF ACTIVATED CHARCOAL[a] OR CIRCULATION THROUGH ACTIVATED CHARCOAL CARTRIDGE.[b] N=3

Time (min)	Charcoal		Activated Charcoal Cartridge	
	ug Barbital/ml WB (mean ± SE)	% of "0" Conc.	ug Barbital/ml WB (mean ± SE)	% of "0" Conc.
Before Barbital	0	--	0	--
0	218.0 ± 0.5	100.0	145.0 ± 0.9	100.0
15	122.0 ± 0.5	56.0	32.0 ± 1.2	22.1
30	120.0 ± 0.5	55.1	17.0 ± 0.5	12.0
45	118.0 ± 0.7	54.1	ND[c]	0.0
60	121.0 ± 0.5	55.5	ND	0.0
75	118.7 ± 0.3	54.4	ND	0.0
90	121.3 ± 0.3	55.6	ND	0.0
105	119.3 ± 0.7	54.7	ND	0.0
120	120.0 ± 0.5	55.1	ND	0.0
135	120.6 ± 0.3	55.3	ND	0.0
150	122.0 ± 0.0	56.0	ND	0.0
165	122.0 ± 0.5	56.0	ND	0.0
180	118.0 ± 0.5	54.1	ND	0.0

[a]Pittsburgh Activated Carbon, a subsidiary of Calgon Corporation, Pittsburgh, Pa.

[b]Becton, Dickinson and Co. Research Center, Research Triangle Park, N. C.

[c]Not detected.

TABLE 2

ETHYLENE GLYCOL (EG) IN WHOLE BLOOD (WB) BEFORE AND AFTER ADDITION OF ACTIVATED CHARCOAL[a] OR CIRCULATION THROUGH ACTIVATED CHARCOAL CARTRIDGE.[b] N=3

Time (min)	Charcoal		Activated Charcoal Cartridge	
	ug EG/ml WB (mean ± SE)	% of "0" Conc.	ug EG/ml WB (mean ± SE)	% of "0" Conc.
Before EG	0	--	0	--
0	518.0 ± 0.8	100.0	573.0 ± 1.4	100.0
15	401.0 ± 1.4	77.4	382.0 ± 5.8	66.7
30	421.3 ± 2.4	81.3	385.0 ± 5.4	67.2
45	401.0 ± 0.5	77.4	385.0 ± 4.5	67.2
60	420.0 ± 0.9	81.0	381.0 ± 1.9	66.5
75	434.3 ± 2.6	83.8	380.0 ± 1.7	66.3
90	420.0 ± 2.8	81.0	381.0 ± 1.9	66.5
105	434.3 ± 2.5	83.8	380.0 ± 1.7	66.3
120	437.0 ± 2.4	84.3	380.0 ± 1.7	66.3
135	420.0 ± 1.3	81.0	380.0 ± 1.7	66.3
150	420.0 ± 1.2	81.0	381.3 ± 1.7	66.5
165	420.0 ± 0.8	81.0	381.0 ± 1.9	66.5
180	417.0 ± 1.4	80.5	376.3 ± 4.3	65.7

[a]Pittsburgh Activated Carbon, a subsidiary of Calgon Corporation, Pittsburgh, Pa.

[b]Becton, Dickinson and Co. Research Center, Research Triangle Park, N. C.

TABLE 3

SODIUM FLUORIDE (NaF) IN WHOLE BLOOD (WB) BEFORE AND AFTER ADDITION OF ACTIVATED CHARCOAL[a] OR CIRCULATION THROUGH ACTIVATED CHARCOAL CARTRIDGE.[b] N=3

Time (min)	Charcoal		Activated Charcoal Cartridge	
	ug NaF/ml WB (mean ± SE)	% of "0" Conc.	ug NaF/ml WB (mean ± SE)	% of "0" Conc.
Before NaF	ND[c]	--	ND	--
0	41.7 ± 0.3	100.0	468.0 ± 0	100.0
15	41.0 ± 0.0	98.3	464.0 ± 0	99.2
30	40.7 ± 0.3	97.6	461.3 ± 2.1	98.7
45	41.0 ± 0	98.3	464.0 ± 0	99.2
60	41.0 ± 0	98.3	461.3 ± 2.1	98.7
75	41.0 ± 0	98.3	461.3 ± 2.1	98.7
90	40.7 ± 0.3	97.6	461.3 ± 2.1	98.7
105	40.3 ± 0.3	96.6	461.3 ± 2.1	98.7
120	41.0 ± 0.0	98.3	464.0 ± 0	99.2
135	40.7 ± 0.3	97.6	461.3 ± 2.1	98.7
150	40.7 ± 0.3	97.6	464.0 ± 0	99.2
165	40.7 ± 0.3	97.6	464.0 ± 0	99.2
180	40.7 ± 0.3	97.6	464.0 ± 0	99.2

[a]Pittsburgh Activated Carbon, a subsidiary of Calgon Corporation, Pittsburgh, Pa.

[b]Becton, Dickinson and Co. Research Center, Research Triangle Park, N. C.

[c]Not detected.

Fig. 1. The in vitro activated charcoal adsorption system showing the closed circuit and ovine blood in a plastic reservoir immersed in a water bath at 37°C.

IN VITRO CARTRIDGE ADSORPTION SYSTEM

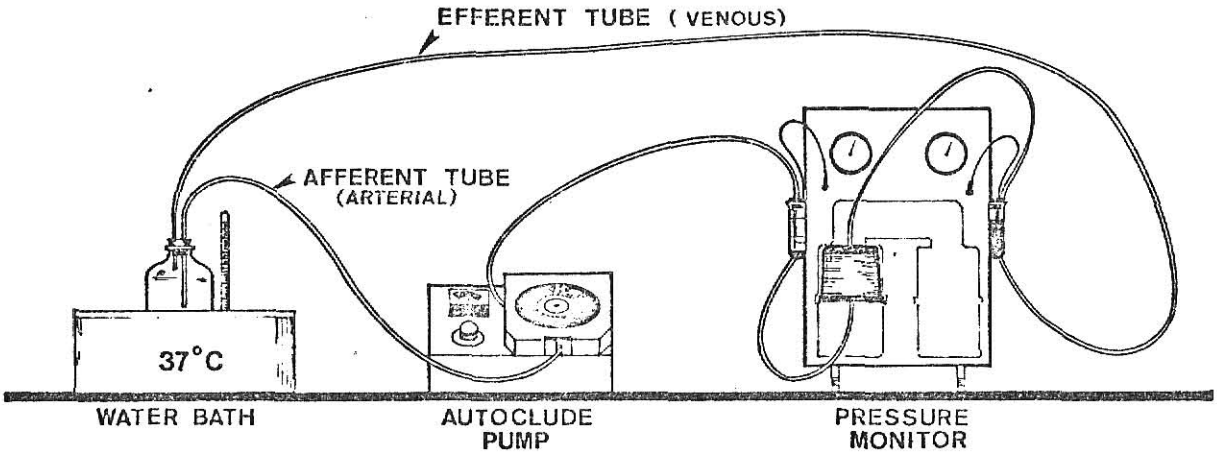


Fig. 2. The percent of initial whole blood or plasma concentrations of barbital, ethylene glycol or sodium fluoride before and after addition of activated charcoal powder to the system.

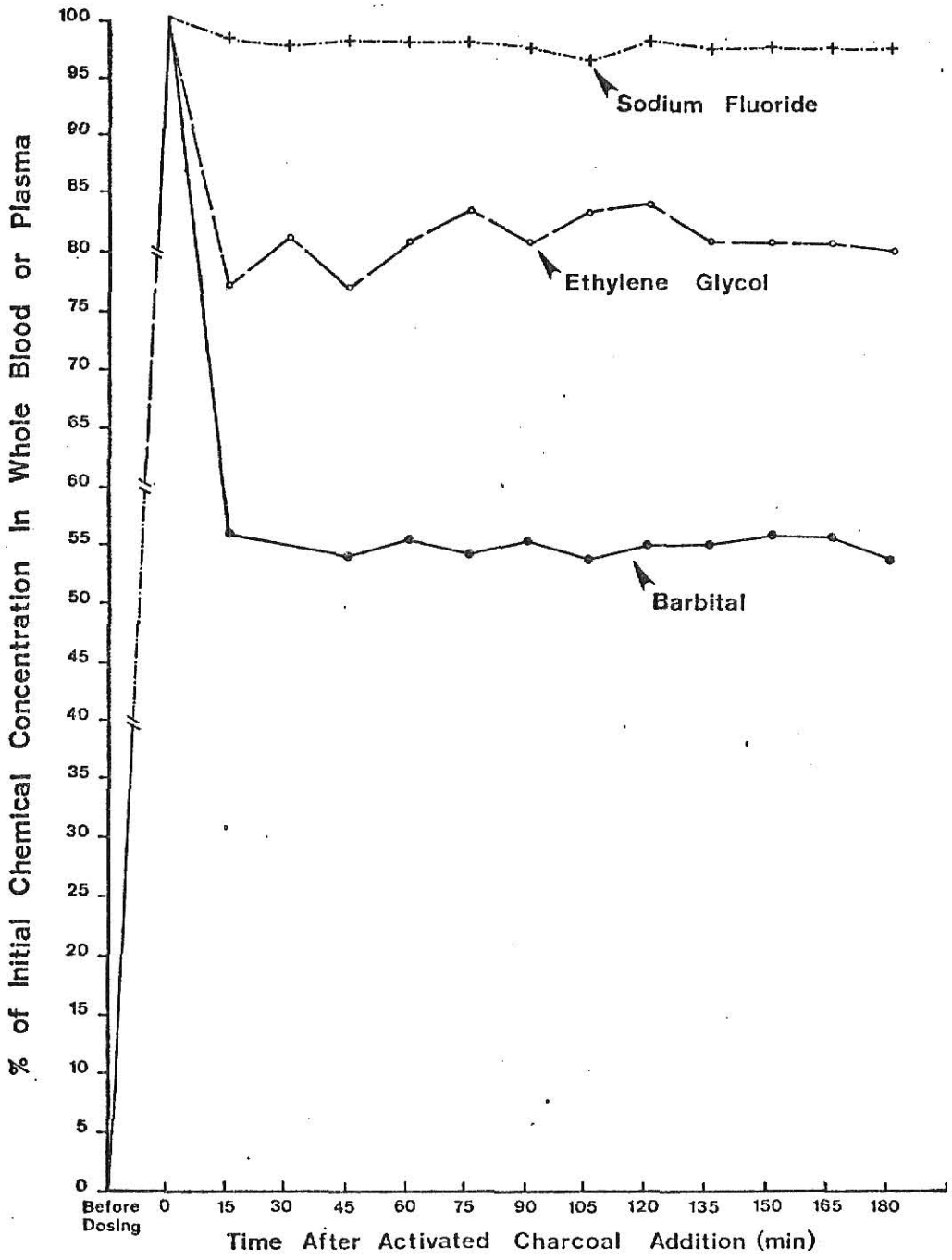
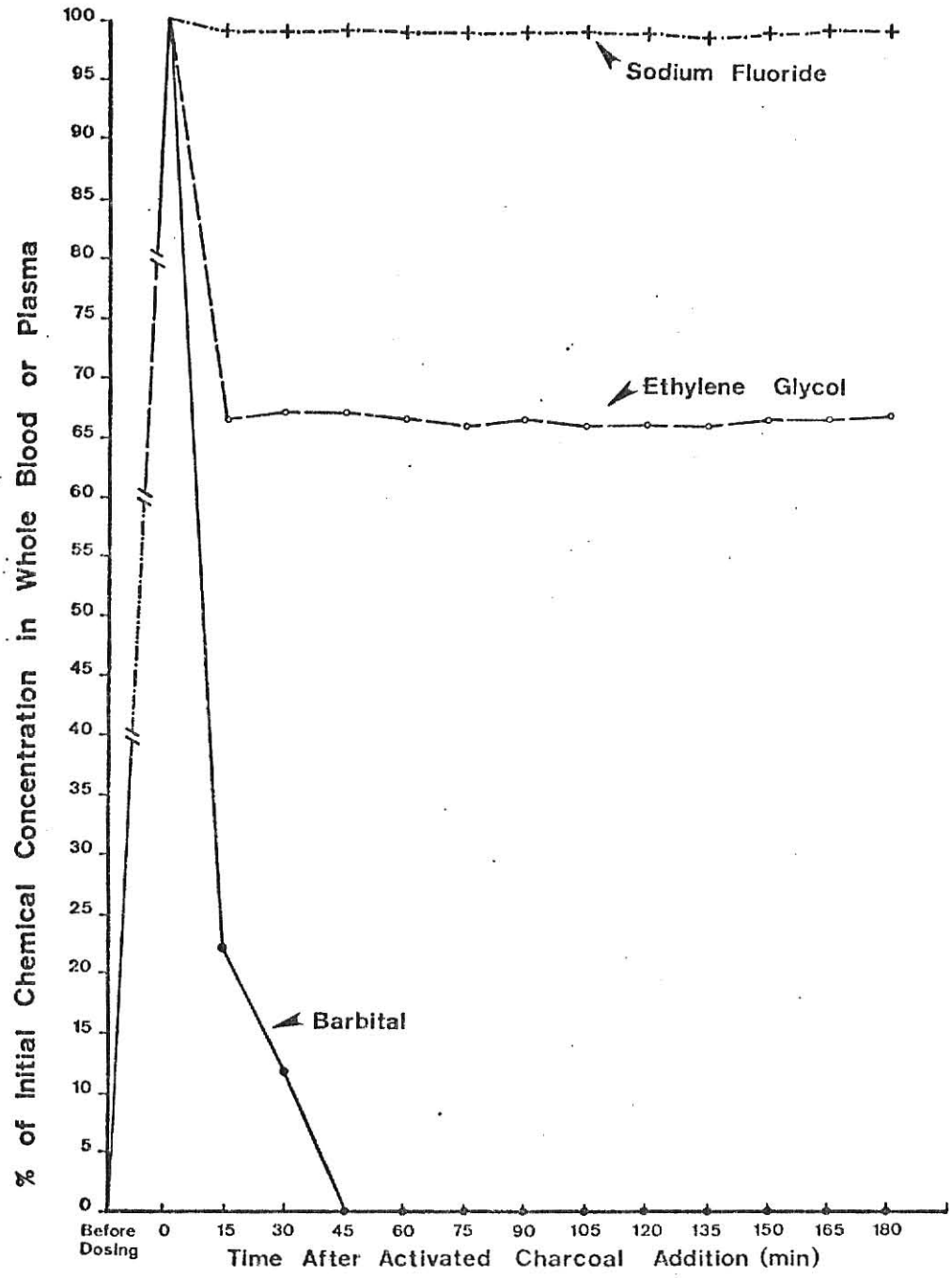

% of Initial Chemical Concentration In Whole Blood or Plasma
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Sodium Fluoride
Ethylene Glycol
Barbital
Before Dosing
0
15
30
45
60
75
90
105
120
135
150
165
180
Time After Activated Charcoal Addition (min)

Fig. 3. The percent of initial whole blood or plasma concentrations of barbital, ethylene glycol or sodium fluoride before and during circulation through the activated charcoal cartridge for 3 hours.


% of Initial Chemical Concentration in Whole Blood or Plasma
100
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Sodium Fluoride
Ethylene Glycol
Barbital
Before Dosing
0
15
30
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60
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90
105
120
135
150
165
180
Time After Activated Charcoal Addition (min)

Index Terms: Barbital, Ethylene glycol, Sodium fluoride, Activated charcoal, Activated charcoal cartridge, Adsorptive affinity, Whole blood

UTILIZATION OF AN ACTIVATED CHARCOAL HEMOPERFUSION SYSTEM FOR THE TREATMENT OF BARBITAL OR ETHYLENE GLYCOL POISONING IN DOGS

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Utilization of an Activated Charcoal Hemoperfusion System for the Treatment of Barbital or Ethylene Glycol Poisoning in Dogs. ADAUDI, A. O. and OEHME, F. W. (197_). Toxicol. Appl. Pharmacol. 00,00-00. The efficacy of activated charcoal (AC) hemoperfusion therapy was studied in dogs acutely poisoned with lethal doses of barbital or ethylene glycol (EG). Two of three barbital-poisoned dogs treated with AC hemoperfusion survived; the dog that died was only hemoperfused for 1½ hr. All the dogs poisoned with EG died, regardless of whether AC hemoperfusion was employed or not. The use of AC hemoperfusion was an effective therapeutic measure for dogs poisoned with lethal doses of barbital.

Activated charcoal (AC) is known to have a broad spectrum for adsorbing various poisons, drugs and metabolites (Adaudi and Oehme, 197_; Corby et al., 1970; Corby and Decker, 1974; Hayden and Comstock, 1975; Holt and Holz, 1963; Picchioni, 1970). Activated charcoal has been used or advocated for use during early stages of poisoning as a gastrointestinal sequestrant of ingested toxicants (Chin et al., 1970; Comstock, 1971; Corby and Decker, 1968, 1974; Crammer and Davies, 1972; Decker et al., 1968a, b; Dordoni and Wilson, 1973; Fane and Decker, 1970; Ferguson, 1970; Furr and Carson, 1975; Gazzard et al., 1974; Levy and Gwilt, 1972; Phansalkar and Holt, 1968).

However, in most instances of poisoning, significant systemic absorption of the toxicant will have occurred before the patient is presented. Earlier studies have shown that hemoperfusion employing an AC cartridge (ACC) can assist in elimination of poisons from the blood (Yatzidis, 1965, 1971; Dunea and Kolff, 1965; Hagstam et al., 1966; DeMyttaenere, et al., 1967). Other workers have used polymer-coated ACC to avoid tissue deposits of particulate charcoal and to enhance biocompatibility (Amdahl, 1975; Andrade, 1972; Chang and Malave, 1970; Chang et al., 1971; Chang et al., 1974; Davis et al., 1974; Gazzard et al., 1974; Sparks et al., 1971, Wilson et al., 1973; Yatzidis, 1971; Kolthamer et al., 1976).

Cases of poisoning by barbiturates and ethylene glycol (EG) have been widespread and sporadic (Penumarthy and Oehme, 1975; Matthew, 1975; Sanyer et al., 1975; Koppanyi and Fazekas, 1950). The current supportive and symptomatic treatment of acute barbiturate intoxication in humans (Matthew, 1975) has been critized (Koppanyi and Fazekas, 1952), and ACC hemoperfusion treatment for barbiturate poisoning is now increasingly

reported (Hagstam et al., 1966; Kolthammer et al., 1976; Rosenbaum, et al. 1968; Widdop et al., 1975; Yatzidis, 1971). The current treatment of EG poisoning involves the use of ethanol and sodium bicarbonate in isotonic saline; treatment is only effective when therapy is initiated in the early stage of toxicosis (Penumarthy and Oehme, 1975; Sanyer et al., 1973). There thus exists a necessity for effective methods of treating EG toxicosis as well as a positive alternative therapy for acute barbiturate poisoning.

Activated charcoal and ACC have been shown to have good adsorptive affinity for barbital, moderate adsorption for EG and poor adsorption for sodium fluoride (Adaudi and Oehme, 197_). However, in vivo studies provide more reliable evidence of AC potential in binding exogenous toxicants (Chin et al., 1973), and in vitro results cannot be accurately extrapolated to ascertain the curative effectiveness of AC or ACC. The present in vivo studies have been conducted to assess the clinical efficacy of ACC hemoperfusion treatment in dogs poisoned with barbital or EG.

METHODS

Materials

Healthy adult male and female mongrel dogs weighing between 9.5 and 21.4 kg (mean weight 16.9 kg $\pm$ 1.3) were used. Commercially purchased barbital[1] and EG[1] were employed. The hemoperfusion system consisted of a pump,[2] pressure monitor,[2] ACC,[2] and a hemoperfusion tubing set (Fig. 1). The ACC contained 100 g of 20 x 50 mesh coconut shell AC and 300 ml of 0.9% sodium chloride and 0.25% glucose solution. One ACC was used in the system except in the case of two EG-poisoned dogs that were treated using two ACC. The hemoperfusion system for the control dogs did not include ACC.

Experimental Design

All dogs were withheld from feed 24 hours prior to starting the experiment. Two to 5 ml of heparinized blood was taken and the animal given acepromazine maleate[4] (1.1 mg/kg body weight) 30 minutes before dosing with barbital or EG to prevent emesis and ease handling.

Each dog was given 330 mg barbital/kg body weight or 8.8 ml EG/kg body weight by stomach tubes. For the barbital experiments, the dogs were intubated with an endotracheal tube and one of the limbs prepared for cannulation surgery when the animal was in a state of deep surgical anesthesia. This occurred about 1 hr after dosing. The patients were then intubated and connected to an oxygen source. The EG-poisoned dogs were anesthetized with thiamylal sodium[5] either 4 or 1 hr after dosing and similarly prepared for hemoperfusion.

The femoral artery and vein of the surgical limb were cannulated with 18 G 2½ inch catheter-needles,[2] and the venous cannula was infused with heparin (100 units/kg body weight). The hemoperfusion system was filled with one liter of sterile physiological saline containing 200 units of heparin. The dogs' blood was circulated through the system at 150 ml/min.

Hemoperfusion of the barbital poisoned dogs was started 1.6 hr $\pm$ 0.2 after dosing. The EG-poisoned dogs had initial hemoperfusion 4.2 hr $\pm$ 0.1 after dosing, but in one EG-poisoned dog hemoperfusion started after 1 hr. Hemoperfusion lasted 3 hr, and blood samples for analysis were taken initially and at 15 min intervals. At the end of the perfusion period, the blood in the tubing was flushed into the patient by pumping non-heparinized physiological saline through the afferent tube. Hemostasis was effected, the surgical incision was sutured, and the patient was returned to the cage after receiving 1-2 ml of an antibiotic combination.[6]

Assay Procedures

Levels of free barbital were determined in 1 ml whole blood by a modified method of Goldbaum (1952); five ml of 0.45N NaOH was used in extracting the barbital from the chloroform aliquot instead of 4 ml. The 1 ug barbital/ml whole blood limit of detection observed in these studies agreed with that determined by Goldbaum (1952) and Kyle et al. (1953). The EG in 1 ml whole blood was determined spectrophotometrically at 555 nm by the method of Harger and Forney (1959). The limit of detection was 72 ug EG/ml.

Statistical Analysis

Mean and SE, correlation coefficient (r^2), and regression lines of the blood concentration (Y) versus time (X) were calculated (Snedcor and Cochran, 1967).

RESULTS

Barbital Poisoned Dogs

The mean barbital blood levels for the control dogs (Table 1) produced the regression formula $Y = 503.75 + 0.5X$ with a coefficient of correlation (r^2) of 0.08. The blood barbital concentrations increased and then remained uniform (Fig. 2). All control dogs remained comatose until death within 19 hr after dosing.

The regression formula for the barbital-poisoned hemoperfused dogs (Table 1) was $Y = 481.09-1.8X$ and r^2 was 0.92. There was a dramatic and continuous drop in the barbital blood levels of the ACC perfused dogs (Fig. 2), although the efficiency of the ACC adsorption gradually decreased with time. Two of the three hemoperfused dogs survived and were normal within three days. The other ACC hemoperfused dog was treated for only 1½ hr because of a

malfunctioning system and died 40 hr after dosing. All the hemoperfused dogs made good clinical improvement during the course of perfusion, as was shown by improved spontaneous respirations and the returning of the pupillary reflex.

Ethylene Glycol Poisoned Dogs

The mean EG blood values are presented in Table 2. The regression formula for the control dog was $Y = 37027.03 + 13.21X$ ($r^2 = 0.52$). The blood EG levels of the control dog continued to rise (Table 2, Fig. 3), no clinical improvement occurred, and death resulted 37 hr after dosing.

For the dogs perfused with 1 ACC 4 hr after dosing, the regression formula was $Y = 36324.07-77.36X$ and $r^2 = 0.89$. The dog perfused with 2 ACC 4 hr after dosing with EG developed blood values that fit the regression formula $Y = 40869.67-104.77X$ with $r^2 = 0.97$, while the dog that was perfused with 2 ACC 1 hr after EG dosing had blood levels that produced the regression formula $Y = 17576.25 + 24.96X$ and $r^2 = 0.93$ (Fig. 3). Although the EG blood levels in the dogs hemoperfused after 4 hr (with 1 or 2 ACC) decreased to 66 and 54% of the initial levels (Table 2), the dogs showed no clinical improvement. A 12% greater decrease in blood EG occurred by using 2 ACC in the system. The dog hemoperfused with 2 ACC 1 hr after dosing had a continuing rise in blood EG (Fig. 3), but the highest concentration of EG detected in the blood approximated the lowest EG concentration found in any of the other hemoperfused dogs (Table 2, Fig. 3). All the dogs remained comatose and died within 19 hr after being dosed with EG.

DISCUSSION

The rapid removal of the barbital from the blood by the ACC hemoperfusion and the clinical recovery of the hemoperfused barbital-

poisoned dogs support earlier observations in human and animals (Yatzidis, 1965; Yatzidis, 1971; Dunea and Kolff, 1965; Hagstam et al., 1966; Kolthammer et al., 1976). The one dog that died due to inadequate hemoperfusion (1½ hr) still survived longer than any of the control dogs.

The decrease in blood EG in dogs perfused with a single ACC was minimal as compared to that observed for barbital. Earlier in vitro experiments (Adaudi and Oehme, 197_) showed that EG was poorly adsorbed by AC; the present data has corroborated this in vivo. Ethyl and methyl alcohol, structural analogues of EG, are also known to be poorly adsorbed by AC (Picchioni, 1970).

Although there was a more pronounced decrease in the EG blood level when two ACC were used, there was no visible clinical effect on the patients. The continually rising blood level of EG in the dog perfused after 1 hr of dosing was probably due to the net effect of continuing EG absorption from the gastrointestinal tract and limited adsorption by the ACC system of the blood EG.

Glucose, free fatty acids and electrolytes are adsorbed from the blood during hemoperfusion (Dunea and Kolff, 1965; Kolthammer et al., 1976). That all the hemoperfused EG-poisoned dogs died quicker than the control may be due to the deleterious effect of this nutrient adsorption by the ACC. This could have offset any beneficial effect of the decrease in EG blood concentration.

These experiments have shown that although AC hemoperfusion can be beneficial in the treatment of barbital poisoning, its use should not be indiscriminate (Matthew, 1975; Leading Article, 1973; Yatzidis, 1972). While poisoning is always an emergency, endorsing the use of AC hemoperfusion for a particular toxicant should be preceded by in vivo experiments to

assess its clinical efficacy for that particular chemical intoxication.

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[2]Becton, Dickinson and Co. Research, Research Triangle Park, N. C.

[3]Cobe Hemmaflo, Cobe Laboratories, Lakewood, Co.

[4]Veterinary Medical Division, Ayerst Laboratories Inc., New York, N. Y.

[5]Parke-Davis & Co., Detroit, Mi.

[6]Combiotic, Pfizer Department of Veterinary Medicine, Chas Pfizer & Co., Inc., New York, N. Y.

TABLE 1

WHOLE BLOOD BARBITAL[a] LEVELS IN DOGS BEFORE AND DURING HEMOPERFUSION WITHOUT (CONTROL) OR WITH ACTIVATED CHARCOAL CARTRIDGE[b] (ACC)

Time (min)	CONTROL (N=2) Mean±SE (ug/ml)	CONTROL (N=2) % of "0" conc.	ACC HEMOPERFUSION (N=3) Mean±SE (ug/ml)	ACC HEMOPERFUSION (N=3) % of "0" conc.
Before Barbital	0	--	0	--
0	487.5±16.6	100.0	561.0±16	100.0
15	504.5± 9.5	103.5	438.0± 9.7	78.1
30	506.0± 0.7	103.8	432.7±16.7	77.1
45	511.5± 4.6	104.9	361.0±11.9	64.3
60	532.5± 9.9	109.2	356.0±14.1	63.5
75	497.5±14.5	102.1	326.3± 7.9	58.2
90	511.5± 4.6	104.9	300.7±14.8	53.6
105	518.5± 9.5	106.4	275.5±11.7	49.1
120	511.5±46.0	104.9	256.0±25.5	45.6
135	498.0[c]	102.2	222.5±12.4	39.7
150	505.0[c]	103.6	209.0±14.8	37.3
165	511.0[c]	104.8	197.0±23.3	35.1
180	518.0[c]	106.3	197.0±80.8	35.1

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Becton, Dickinson & Co. Research Center, Research Triangle Park, N. C.

[c]N=1.

TABLE 2

WHOLE BLOOD ETHYLENE GLYCOL[a] (EG) LEVELS IN DOGS BEFORE AND DURING HEMOPERFUSION WITHOUT (CONTROL) OR WITH 1 OR 2 ACTIVATED CHARCOAL CARTRIDGE[b] (ACC) 4 OR 1 HOUR AFTER DOSING

	CONTROL (N=1)		ACC HEMOPERFUSION					
			1 cartridge 4 hr after dosing (N=2)		2 cartridge 4 hr after dosing (N=1)		2 cartridge 1 hr after dosing (N=1)	
Time (min)	Mean (ug/ml)	% of "0" conc.	Mean±SE (ug/ml)	% of "0" conc.	Mean (ug/ml)	% of "0" conc.	Mean (ug/ml)	% of "0" conc.
Before EG	0	--	0	--	0	--	0	--
0	36060	100.0	36615±.006	100.0	39770	100.0	17600	100.0
15	37740	104.7	38030±.004	103.9	38320	96.4	18160	103.2
30	37180	103.1	35195±.008	96.1	37180	93.5	18730	106.4
45	37490	104.0	32640±.006	89.1	36040	90.6	18730	106.4
60	39170	108.6	29805±.01	81.4	36040	90.6	18730	106.4
75	38360	106.4	29235±.02	79.8	34340	86.3	18730	106.4
90	37740	104.7	27670±.12	75.6	32640	82.1	19300	109.7
105	37180	103.1	26990±.008	73.7	31220	78.5	20430	116.0
120	39470	109.5	26110±.01	71.3	28950	72.8	21000	119.3
135	39170	108.6	24405±.008	66.6	24980	62.8	21000	119.3
150	39470	109.5	25685±.001	70.1	24410	61.4	21570	122.6
165	39170	108.6	24915±.006	68.0	23270	58.5	22140	125.8
180	38610	107.1	24410±.004	66.7	21570	54.2	21570	122.6

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Becton, Dickinson & Co. Research Center, Research Triangle Park, N. C.

Fig. 1. The in vivo activated charcoal hemoperfusion system. The patient's femoral artery is connected to the afferent tubing and the efferent tubing returns to the femoral vein of the same limb.

IN VIVO HEMOPERFUSION SYSTEM

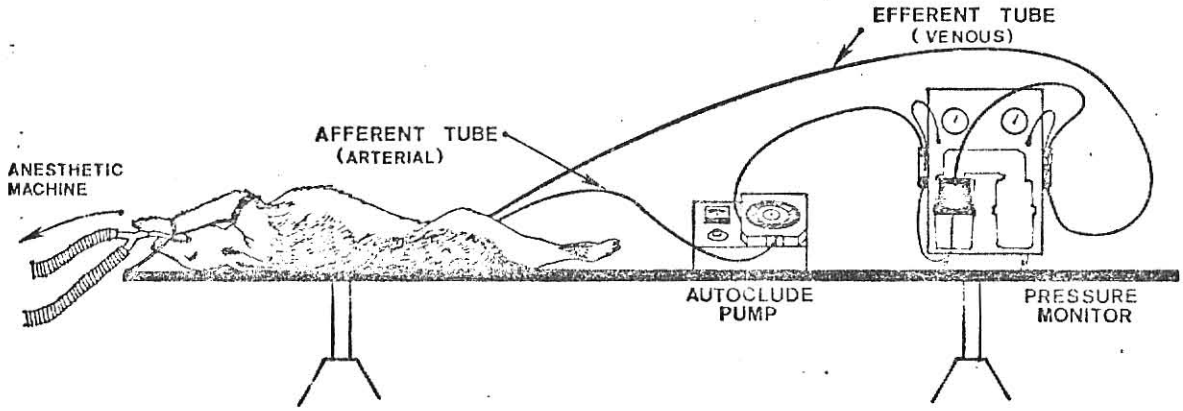


Fig. 2. Whole blood levels of barbital during hemoperfusion with or without activated charcoal cartridge.

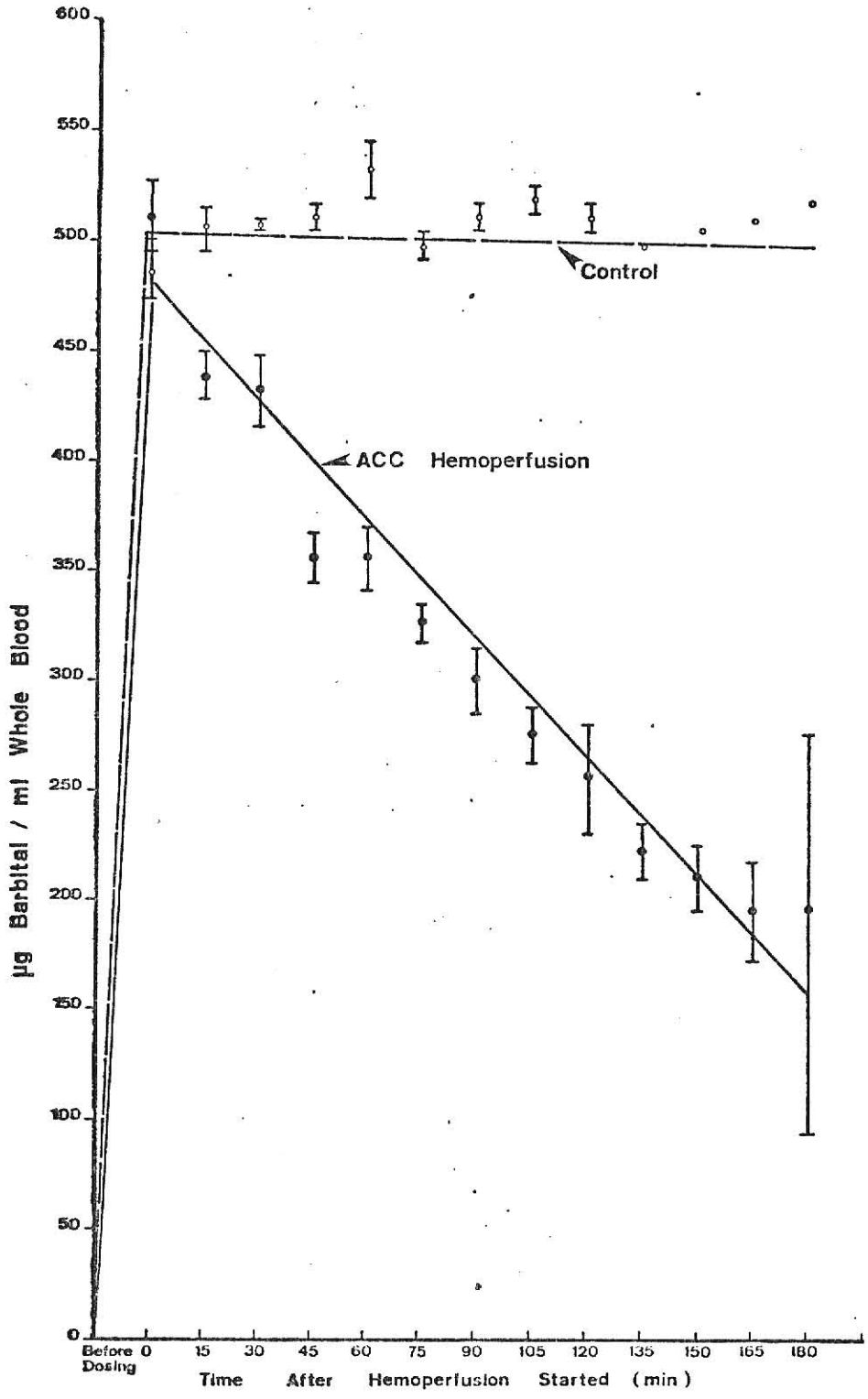
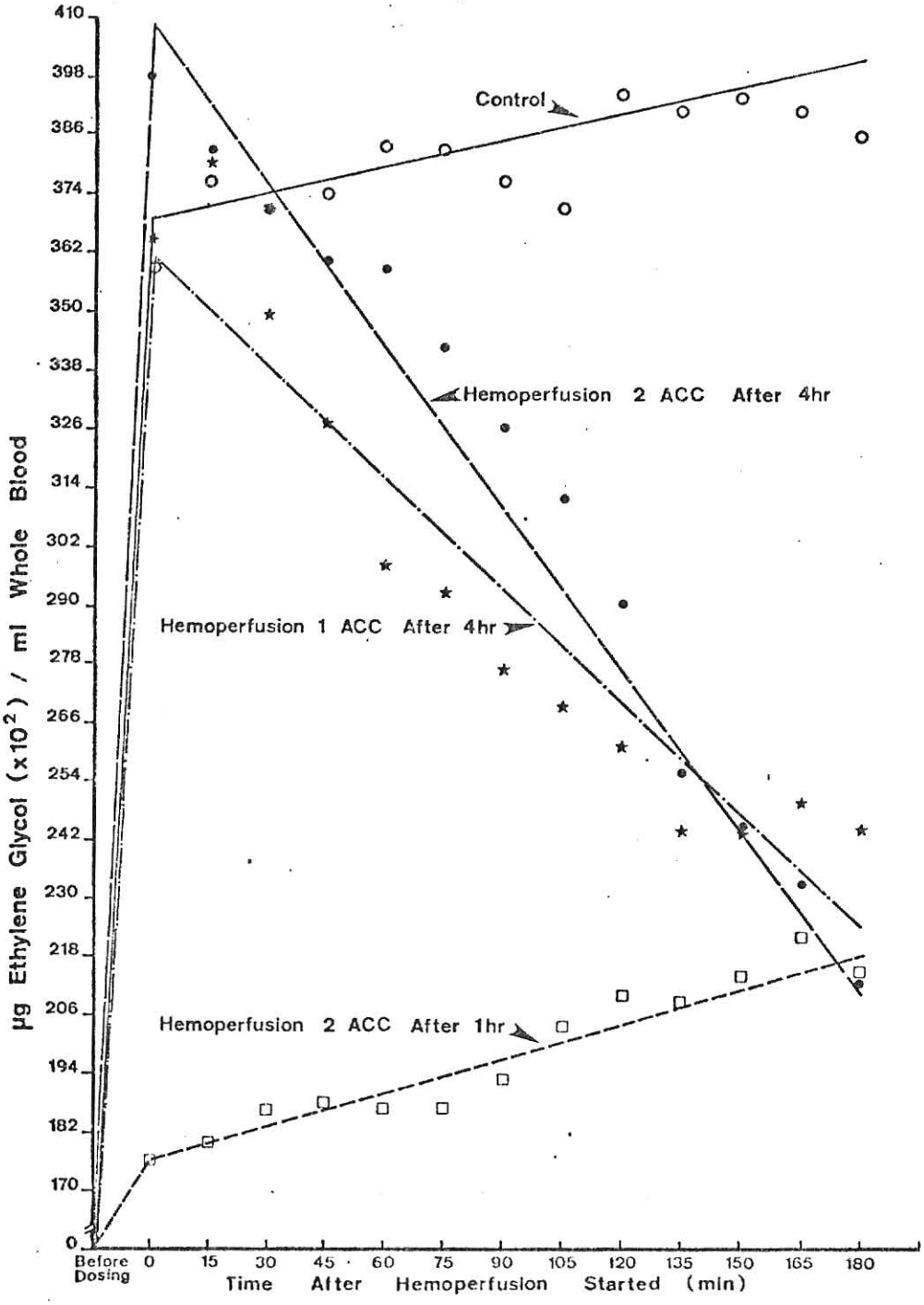

600
550
500
450
400
350
300
250
200
150
100
50
0
µg Barbital / ml Whole Blood
Control
ACC Hemoperfusion
Before Dosing
0
15
30
45
60
75
90
105
120
135
150
165
180
Time After Hemoperfusion Started (min)

Fig. 3. Whole blood levels of ethylene glycol during hemoperfusion with or without activated charcoal cartridge.


410
398
386
374
362
350
338
326
314
302
290
278
266
254
242
230
218
206
194
182
170
0
µg Ethylene Glycol (x10²) / ml Whole Blood
Control
Hemoperfusion 2 ACC After 4hr
Hemoperfusion 1 ACC After 4hr
Hemoperfusion 2 ACC After 1hr
Before Dosing
0
15
30
45
60
75
90
105
120
135
150
165
180
Time After Hemoperfusion Started (min)

Index Terms: Barbital, Ethylene glycol, Poisoning, Dogs, Treatment, Activated charcoal, Activated charcoal cartridge, Hemoperfusion

APPENDIX A

EXPERIMENTAL DATA

BARBITAL

Standard Curve

The standard curve obeys Beer's Law from 2-30 ug barbital/ml whole blood (Table A1). Figure A1 is an illustration of the barbital standard curve.

Limit of Sensitivity

The limit of sensitivity of the spectrophotometer (Coleman 124 Double Beam, Hitachi Perkin-Elmer) was 1 ug barbital/ml whole blood.

Percentage Recovery

The mean recovery was 81.3% $\pm$ 10.3 (SE). Table A2 provides recovery data for barbital.

TABLE A1

RELATIONSHIP BETWEEN OPTICAL DENSITY DIFFERENCES[a] AT 260 nm AND BARBITAL[b] CONCENTRATIONS IN WHOLE BLOOD (WB)[c]

Barbital (ug/ml WB)	Optical Density Difference
10	0.019
20	0.050
40	0.115
60	0.165
80	0.245
100	0.287
120	0.352
140	0.432
160	0.497
180	0.500
120	0.587

[a]Optical density differences of barbital standards in 0.45N NaOH at pH 12.5 and 10.5 (Goldbaum, 1952).

[b]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[c]Freshly collected heparinized canine blood.

TABLE A2

PERCENTAGE RECOVERY OF BARBITAL[a] FROM WHOLE BLOOD (WB)

Barbital Added (ug/ml WB)	Barbital recovered (ug/ml WB)	Recovery %
10	5.59	55.9
20	14.71	73.6
40	33.82	84.46
60	48.33	80.09
80	72.06	90.01
100	75.0	75.0
120	103.55	86.3
140	127.06	90.08
160	146.18	91.4
180	147.06	81.17
200	172.65	86.63

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

TABLE A3

IN VITRO WHOLE BLOOD (WB) BARBITAL[a] LEVELS
BEFORE AND AFTER ADDITION OF
ACTIVATED CHARCOAL[b]

Time (min)	ug Barbital/ml WB				% of "0" Conc.
	Trial 1	Trial 2	Trial 3	Mean ± SE	
Before barbital added	0	0	0	0	--
0	217	218	219	218.0 ± 0.5	100.0
15	123	122	121	122.0 ± 0.5	56.0
30	121	120	119	120.0 ± 0.5	55.1
45	117	118	120	118.0 ± 0.7	54.1
60	120	121	122	121.0 ± 0.5	55.5
75	118	119	119	118.7 ± 0.3	54.4
90	121	122	121	121.3 ± 0.3	55.6
105	121	118	119	119.3 ± 0.7	54.7
120	121	120	119	120.0 ± 0.5	55.1
135	121	121	120	120.6 ± 0.3	55.3
150	122	122	122	122.0 ± 0.0	56.0
165	121	123	122	122.0 ± 0.5	56.0
180	119	118	117	118.0 ± 0.5	54.1

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Pittsburgh Activated Carbon, a subsidiary of Calgon Corporation, Pittsburgh, Pa.

TABLE A4

IN VITRO WHOLE BLOOD (WB) BARBITAL[a] LEVELS BEFORE AND DURING CIRCULATION THROUGH ACTIVATED CHARCOAL CARTRIDGE[b]

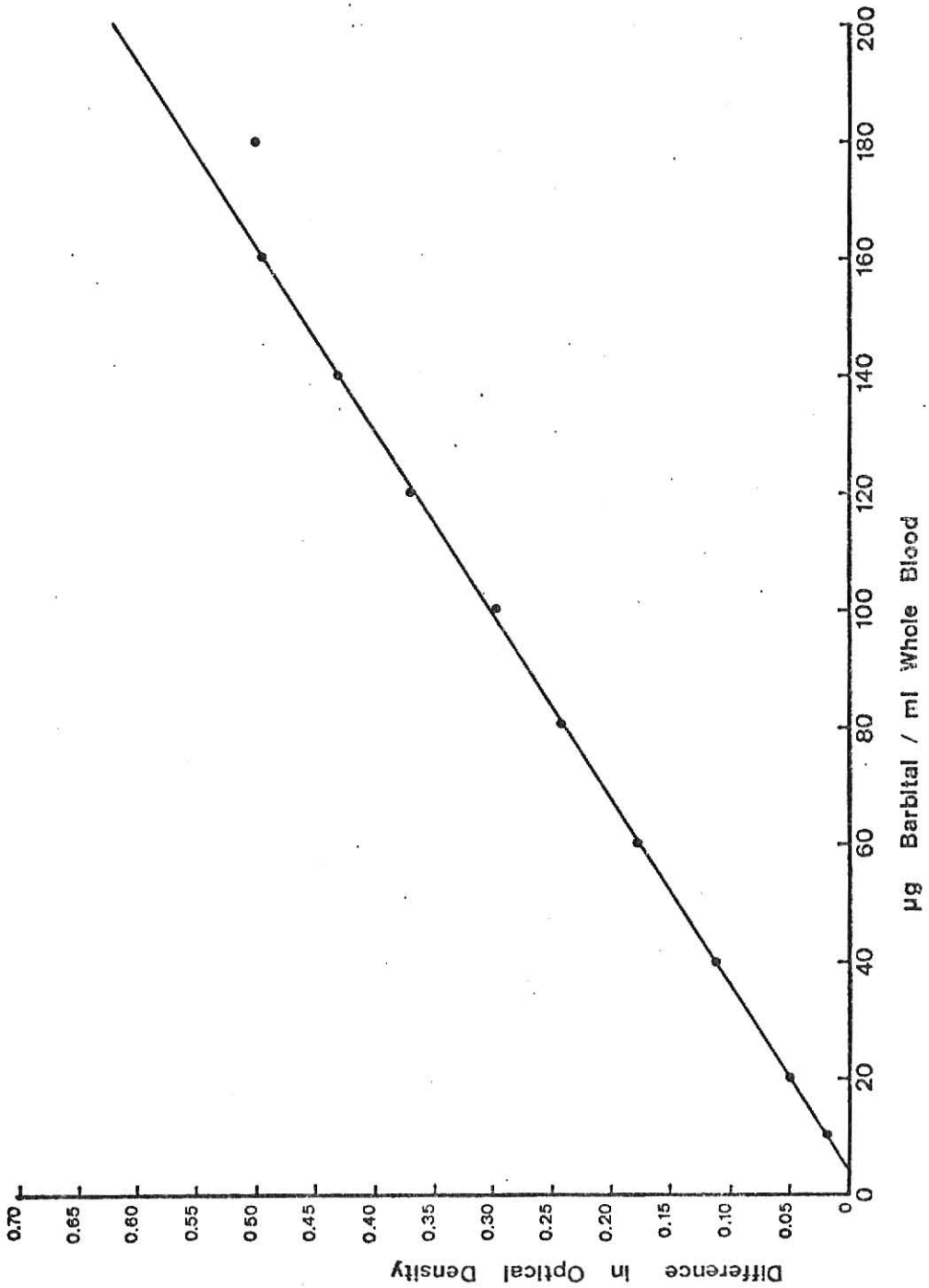
Time (min)	ug Barbital/ml WB				
	Trial 1	Trial 2	Trial 3	Mean ± SE	% of "0" Conc.
Before barbital added	0	0	0	0	--
0	145	143	147	145 ± 0.9	100.0
15	35	30	31	32 ± 1.2	22.1
30	18	17	16	17 ± 0.5	12.0
45	ND[c]	ND	ND	ND	0.0
60	ND	ND	ND	ND	0.0
75	ND	ND	ND	ND	0.0
90	ND	ND	ND	ND	0.0
105	ND	ND	ND	ND	0.0
120	ND	ND	ND	ND	0.0
135	ND	ND	ND	ND	0.0
150	ND	ND	ND	ND	0.0
165	ND	ND	ND	ND	0.0
180	ND	ND	ND	ND	0.0

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Becton, Dickinson and Co. Research Center, Research Triangle Park, N. C.

[c]Not detected.

Fig. A1. Standard Curve Expressing the Relationship of Optical Density Differences (260 nm) to Barbital Concentration (ug/ml Whole Blood). The Optical Density Used is the Difference in Optical Density Readings in 0.45N NaOH at pH 12.5 and pH 10.5 (Goldbaum, 1952).


Difference in Optical Density
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
20
40
60
80
100
120
140
160
180
200
µg Barbital / ml Whole Blood

ETHYLENE GLYCOL (EG)

Standard Curve

The standard curve does not obey Beer's Law throughout the range used (see Table A5 and Fig. A2).

Limit of Sensitivity

The limit of sensitivity of the spectrophotometer (Coleman 124 Double Beam, Hitachi Perkin-Elmer) was 72 ug EG/ml whole blood.

Percentage Recovery

The mean recovery for EG was 83.3% $\pm$ 3.5 at a concentration of 300 ul EG/l whole blood and was 67.0% $\pm$ 1.8 at a concentration of 700 ul EG/l whole blood (see Table A6).

TABLE A5

RELATIONSHIP BETWEEN OPTICAL DENSITIES AT 555 nm AND ETHYLENE GLYCOL[a] (EG) CONCENTRATIONS IN WHOLE BLOOD (WB)[b]

EG (ul/l WB)	Optical Density
100	0.025
200	0.098
300	0.165
400	0.330
500	0.520
600	0.690
700	0.855

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Freshly collected heparinized canine blood.

TABLE A6

PERCENT RECOVERY OF ETHYLENE GLYCOL[a] (EG) FROM WHOLE BLOOD (WB)

EG added (ul/1 WB)	EG recovered (ul/1 WB)	Recovery (%)	
300	265	88.3	83.3 ± 3.5
300	235	78.3	
700	500	71.4	
700	450	64.3	67.0 ± 1.8
700	460	65.7	

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

TABLE A7

IN VITRO WHOLE BLOOD (WB) ETHYLENE GLYCOL[a] (EG) LEVELS BEFORE AND AFTER ADDITION OF ACTIVATED CHARCOAL[b]

Time (min)	ug EG/ml WB				
	Trial 1	Trial 2	Trial 3	Mean ± SE	% of "0" Conc.
Before EG added	0	0	0	0	--
0	517	517	520	518.0 ± 0.8	100.0
15	404	401	398	401.0 ± 1.4	77.4
30	427	420	417	421.3 ± 2.4	81.3
45	400	401	402	401.0 ± 0.5	77.4
60	420	418	422	420.0 ± 0.9	81.0
75	498	404	401	434.3 ± 2.6	83.8
90	414	420	426	420.0 ± 2.8	81.0
105	496	403	404	434.3 ± 2.5	83.8
120	496	406	409	437.0 ± 2.4	84.3
135	421	422	417	420.0 ± 1.3	81.0
150	419	418	423	420.0 ± 1.2	81.0
165	419	419	422	420.0 ± 0.8	81.0
180	414	417	420	417.0 ± 1.4	80.5

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Pittsburgh Activated Carbon, a subsidiary of Calgon Corporation, Pittsburgh, Pa.

TABLE A8

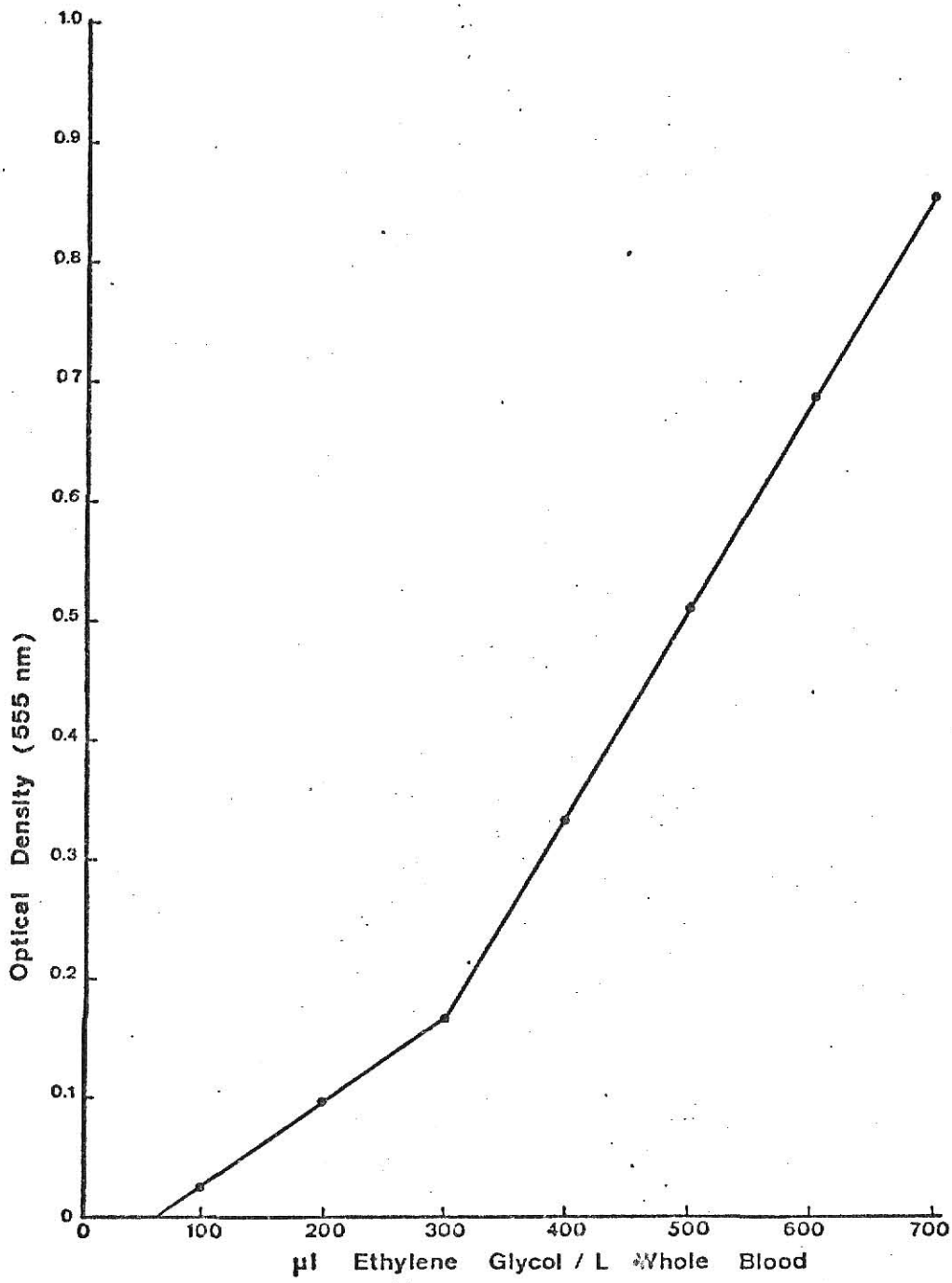
IN VITRO WHOLE BLOOD (WB) ETHYLENE GLYCOL[a] (EG) LEVELS BEFORE AND DURING CIRCULATION THROUGH ACTIVATED CHARCOAL CARTRIDGE[b]

Time (min)	ug EG/ml WB				
	Trial 1	Trial 2	Trial 3	Mean ± SE	% of "0" Conc.
Before EG added	0	0	0	0	--
0	570	573	576	573.0 ± 1.4	100.0
15	369	386	393	382.0 ± 5.8	66.7
30	376	381	398	385.0 ± 5.4	67.2
45	378	381	396	385.0 ± 4.5	67.2
60	377	381	385	381.0 ± 1.9	66.5
75	377	381	384	380.0 ± 1.7	66.3
90	377	381	385	381.0 ± 1.9	66.5
105	377	381	384	380.0 ± 1.7	66.3
120	377	381	384	380.0 ± 1.7	66.3
135	377	381	384	380.0 ± 1.7	66.3
160	378	381	385	381.3 ± 1.7	66.5
165	377	381	385	381.0 ± 1.9	66.5
180	377	367	385	376.3 ± 4.3	67.7

[a]Fisher Scientific Company, Chemical Manufacturing Division, Fair Lawn, N. J.

[b]Becton, Dickinson and Co. Research Center, Research Triangle Park, N. C.

Fig. A2. Relationship Between Optical Density (555 nm) and Ethylene Glycol Concentrations (ul/l Whole Blood).


Optical Density (555 nm)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
100
200
300
400
500
600
700
µl Ethylene Glycol / L Whole Blood

SODIUM FLUORIDE (NaF)

Standard Curve

A straight line results from values produced by reading the mv detected by an Orion fluoride ion-specific electrode in NaF standard solution containing from 1 to 100 ppm fluoride. The line was plotted on semi-logarithmic paper (4 cycles x 70 divisions).

Limit of Sensitivity

The limit of sensitivity of the fluoride electrode when used with an Orion Model 701 Digital pH/mV Meter was 1 ug/ml whole blood (Orion, 1975).

Comparison of Deionized Water with Plasma

Table A9 and Fig. A3 present the data comparing NaF detection in deionized water and plasma. The detection capability was identical in both media.

Percentage Recovery

The mean recovery of NaF was 99.1% $\pm$ 0.2 with a concentration of 100 ug/ml and was 103.0% $\pm$ 0.40 when a concentration of 1 ug NaF/ml was used (Table A10).

TABLE A9

MILLIVOLT[a] READINGS RESULTING FROM STANDARD CONCENTRATIONS OF SODIUM FLUORIDE[b] PREPARED IN PLASMA OR DEIONIZED WATER

Sodium Fluoride (ppm)	Millivolts (+)	
	Deionized Water	Plasma
1	118.4	117.4
2	101.9	100.9
3	92.8	92.4
5	79.8	79.5
10	62.4	62.1
20	44.6	44.5
50	21.8	21.6
100	4.6	4.5

[a]Expanded Scale mv using Model 701 pH/mv digital meter.

[b]Sodium Fluoride Powder, Mallinckrodt Chemical Works, St. Louis, Mo.

TABLE A10

PERCENT RECOVERY OF SODIUM FLUORIDE[a] (NaF)
FROM WHOLE BLOOD (WB)

NaF added (ug/ml WB)	NaF recovered (ug/ml WB)	Recovery (%)	
1	1.04	104.0	
1	1.02	102.0	
1	1.04	104.0	103.0 ± 0.4
1	1.02	102.0	
1	1.03	103.0	
100	98.5	98.5	
100	99.0	99.0	
100	99.0	99.0	99.1 ± 0.2
100	99.5	99.5	
100	99.7	99.7	

[a]Mallinckrodt Chemical Works, St. Louis, Mo.

TABLE A11

IN VITRO WHOLE BLOOD (WB) SODIUM FLUORIDE[a] (NaF) LEVELS BEFORE AND AFTER ADDITION OF ACTIVATED CHARCOAL[b]

Time (min)	ug NaF/ml WB				
	Trial 1	Trial 2	Trial 3	Mean ± SE	% of "0" Conc.
Before NaF added	ND[c]	ND	ND	ND	--
0	41	42	42	41.7 ± 0.3	100.0
15	41	41	41	41.0 ± 0.0	98.3
30	41	41	40	40.7 ± 0.3	97.6
45	41	41	41	41.0 ± 0.0	98.3
60	41	41	41	41.0 ± 0.0	98.3
75	41	41	41	41.0 ± 0.0	98.3
90	41	40	41	40.7 ± 0.3	97.6
105	40	41	41	40.3 ± 0.3	96.6
120	41	41	41	41.0 ± 0.0	98.3
135	41	40	41	40.7 ± 0.3	97.6
150	40	41	41	40.7 ± 0.3	97.6
165	41	40	41	40.7 ± 0.3	97.6
180	40	41	41	40.7 ± 0.3	97.6

[a]Mallinckrodt Chemical Works, St. Louis, Mo.

[b]Pittsburgh Activated Carbon, a subsidiary of Calgon Corporation, Pittsburgh, Pa.

[c]Not detected.

TABLE A12

IN VITRO WHOLE BLOOD (WB) SODIUM FLUORIDE[a] (NaF) LEVELS BEFORE AND DURING CIRCULATION THROUGH ACTIVATED CHARCOAL CARTRIDGE[b]

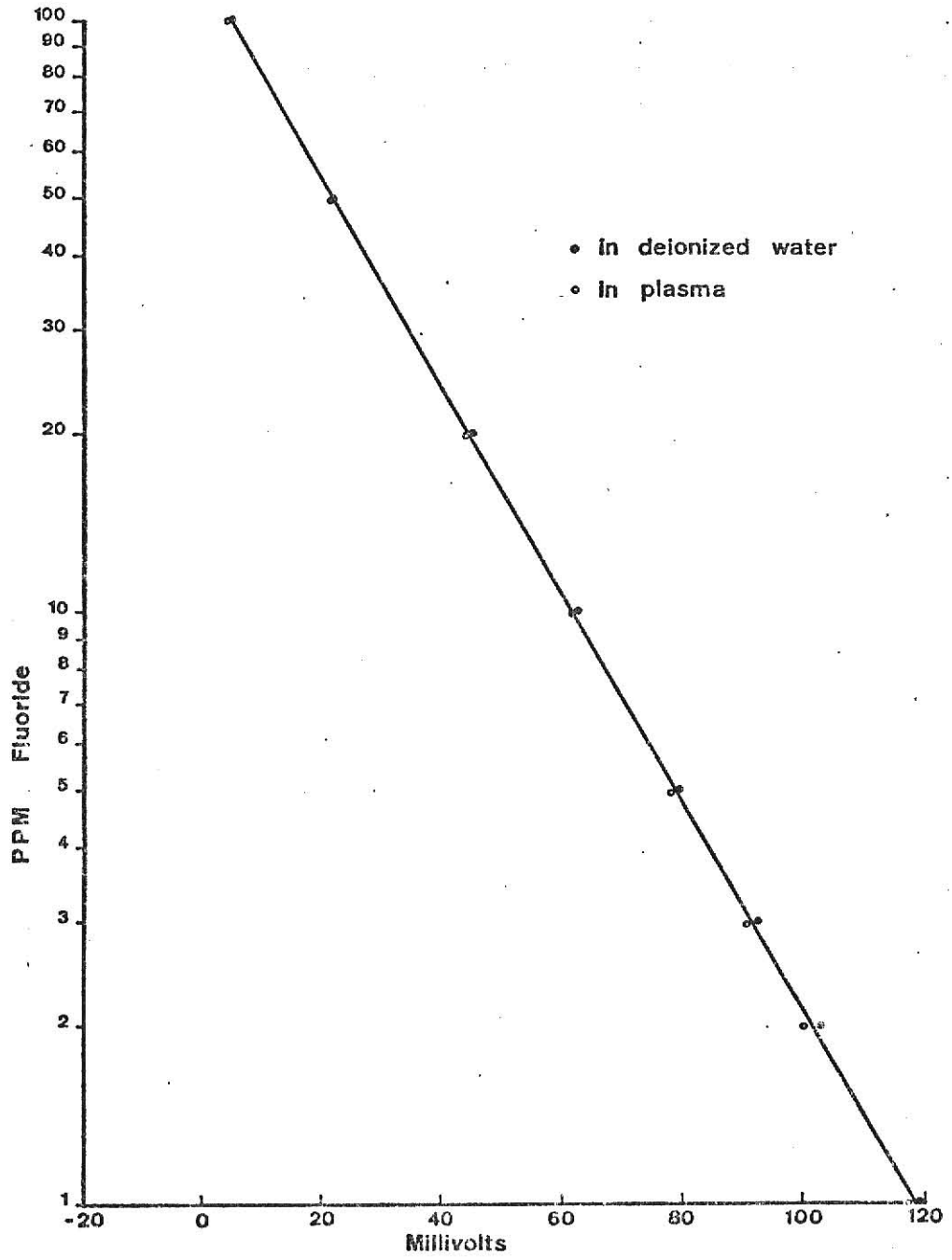
Time (min)	ug NaF/ml WB				% of "0" Conc.
	Trial 1	Trial 2	Trial 3	Mean ± SE	
Before NaF added	ND[c]	ND	ND	ND	--
0	468	468	468	468.0 ± 0.0	100.0
15	464	464	464	464.0 ± 0	99.2
30	456	464	464	461.3 ± 2.1	98.7
45	464	464	464	464.0 ± 0	99.2
60	456	464	464	461.3 ± 2.1	98.7
75	464	464	456	456.0 ± 2.1	98.7
90	464	456	464	461.0 ± 2.1	98 7
105	464	456	464	461.0 ± 2.1	98.7
120	464	464	464	464.0 ± 0	99.2
135	456	464	464	461.3 ± 2.1	98.7
150	464	464	464	464.0 ± 0	99.2
165	464	464	464	464.0 ± 0	99.2
180	464	464	464	464.0 ± 0	99.2

[a] Mallinckrodt Chemical Works, St. Louis, Mo.

[b] Becton, Dickinson and Co. Research Center, Research Triangle Park, N. C.

[c] Not detected.

Fig. A3. Plot of Milliovolt Readings for Standard Concentrations of Fluoride in Deionized Water or Plasma.


100
90
80
70
60
50
40
30
20
10
9
8
7
6
5
4
3
2
1
PPM Fluoride
-20
0
20
40
60
80
100
120
Millivolts
• in deionized water
◦ in plasma

APPENDIX B

BARBITURATE TOXICOSIS AND THERAPY

A LITERATURE REVIEW

BARBITURATE TOXICOSIS AND THERAPY

A LITERATURE REVIEW

INTRODUCTION

There are conflicting historical accounts about the early preparations of barbituric acid (Aviado, 1972; Gleason et al., 1969; Matthew, 1975; and Myschetzky, 1971). Aviado (1972) claimed that Conrad and Guthzert prepared barbituric acid from the condensation of urea and malonic acid in 1882 while Matthew (1975) and Myschetzky (1971) claimed that it was Von Baeyer who synthesized barbituric acid in 1864.

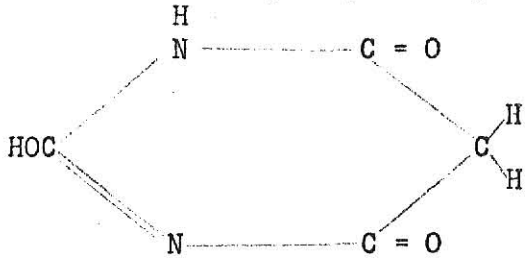
Barbituric acid is not itself a hypnotic. Barbital, the first central nervous system depressant, was prepared by Fischer and Von Mering in 1903; phenobarbital was synthesized by Hoerlein in 1911; and the first higher molecular weight barbituric acid derivatives were made by Shonle in 1916. Since then chemists have synthesized and tested hundreds of new derivatives of which several dozen are now in current clinical use.

In their account, Casarett and Doull (1975) claim barbituric acid was first synthesized in 1863 and that the first central nervous system depressant was prepared in 1882, although it was not clinically used until 1903.

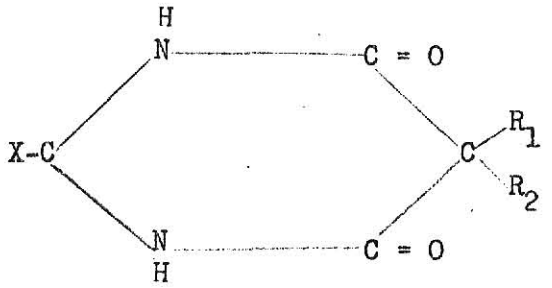
CHEMISTRY

Barbituric acid is a cyclic ureide composed of a pyrimidine nucleus resulting from the condensation of urea and malonic acid. The replacement of the two hydrogens on carbon 5 by various radicals, such as oxygen, cyclic radical, or sulphur, produces a series of central nervous

system depressants known as oxybarbiturates, spirobarbiturates and thiobarbiturates, respectively.



Barbituric acid



X = O or S

General formula of barbiturates

PHYSICAL AND CHEMICAL PROPERTIES

Oxybarbiturates are white powders while the thiobarbiturates are yellow. The average melting point is between 100 and 200°C. Although barbituric acid is a weak acid, the sodium salts are highly alkaline (pH up to 11), very soluble in water, freely soluble in alcohol, and practically insoluble in ether. Solutions of barbiturates are unstable, and they will decompose on standing at room temperature and more quickly if heated. Barbiturates have been grouped into four classes on the basis of the duration of their hypnotic or anesthetic activities.

I. Long duration of action (8-12 hours); e.g. barbital, phenobarbital.

II. Moderate duration of action (2-8 hours); e.g. Amobarbital (Amytal).

III. Short duration of action (1-4 hours); e.g. pentobarbital.

IV. Ultrashort duration of action (5-30 minutes); e.g. Thiamylal (Surital) and Thiopental (Pentotal) sodium.

USES OF BARBITURATES

Barbiturates are used in human medicine for hypnosis or heavy

sedation, to antagonize convulsions from stimulating drugs, as basal anesthetics, in psychiatric interviews (narco-interrogations), and for preanesthetic agents (Adriani, 1970; Matthew, 1975).

In veterinary medicine, pentobarbital sodium is widely used as a surgical anesthetic in various species. In the United States and most other countries, it is the most widely used anesthesia in dogs and cats (Jones, 1965). Some dogs show after-effects, such as whinning, barking, and running movements.

In large animal practice, the use of sodium pentobarbital alone or in combination for surgical anesthesia has significantly increased. In swine and goats pentobarbital sodium has been used as a general anesthetic or as a sedative followed by local anesthetics (Danks, 1943; Kernkamp, 1939; Jones, 1965; Wright, 1939; Allam and Churchill, 1946). Sodium pentobarbital anesthesia in exotic, wild or zoo animals have been induced in mink by the subcutaneous route (Fuhrmann and Stuhr, 1941), in chimpanzees rectally (Elder, 1937), and in bears intravenously (Clifford et al., 1962).

There are other important nonsurgical veterinary uses of pentobarbital sodium. These include its effective use to counteract the convulsive effects of strychnine poisoning (Barlow, 1937), to suppress acute seizures or status epilepticus in dogs (Upson, 1975), for euthanasia (Jones, 1965), and to speed the excretion of undesirable chemical residues in food animals (Braund et al., 1970).

TOXICITY

The nonjudicious use or abuse of barbiturates can result in poisoning of human and animal patients. The drug is contraindicated in hepatic diseases, shock or shock-like states, porphyria, Parkinsonism

and pregnancy (Adriani, 1970; Dreisbach and Synder, 1943; Sessions et al., 1954).

Acute barbiturate overdosage resulting from automatism, suicide and parasuicide (Kennedy, 1972), together with the chronic dependance and withdrawal effects in humans, have prompted many to advocate restriction of their use to utilizing their anticonvulsant properties only (Leader, 1971; McQueen, 1970; Tylden and Saville, 1970; Wells, 1970). Acute barbiturate poisoning is regarded as the most widespread cause of human intoxication, resulting in about 1500 deaths annually in the United States (Casarett and Doull, 1975; Gleason et al., 1969). In 1954-1956 70% of all admissions to the Poison Treatment Center at Copenhagen was due to barbiturate, while in 1965 barbiturate overdosage accounted for 50% of the admissions to the Edinburgh Poisoning Treatment Center; this figure was 30% lower in 1968 (Myschetzky, 1971).

In a review of drug abuse in 252 admissions to the Edinburgh Poisoning Treatment Center during 1971 and 1972, barbiturates were the drugs most often abused (Forrest and Tarala, 1973). Barbiturates are known to be the most commonly taken drugs in self-poisonings or automatism (Casarett and Doull, 1975, Matthew et al., 1969).

In veterinary medicine, barbiturate overdosage can be of iatrogenic origin or intentional. Concurrent diseases of the kidney or liver, incorrect dosing, species variation, and individual idiosyncratic reactions are predisposing factors to barbiturate poisoning in domestic animals. Cats show "reverse tolerance" to repeated doses of barbiturates (Upson, 1975).

CLINICAL SIGNS

The clinical signs and severity of barbiturate poisoning varies

with chemical factors, such as the type and quantity of drug absorbed, interractions with other drugs, and biologic factors, such as species or individual variations and concurrent diseases present.

The most important clinical effects have been described (Hall, 1971; Matthew, 1975; Moeschlin, 1971) and include respiratory depression, impaired level of consciousness, cardiovascular damage, and hypothermia. Lesser significant signs are those involving the skin, gastrointestinal tract, renal and hepatic systems. Death in acute barbiturate poisoning is due to either cessation of respiration resulting from depression of respiratory center, or cardiovascular depression, or the consequences of prolonged unconsciousness (Lington and Ledingham, 1966).

Respiratory

Respiratory depression causing a minute volume of less than 4 liters is considered severe (Matthew, 1975). Other infrequent respiratory effects include pulmonary edema, secondary bacterial infections, and barbiturate inhalation into the lungs as a result of vomiting or injudicious or unskilled gastric aspiration and lavage (Moeschlin, 1971).

Level of Consciousness

This is determined by various permutations and combinations of reflexes. The level of consciousness ranges from sedation through hypnosis to basal anesthesia, surgical anesthesia, and euthanasia.

Cardiovascular System

Barbiturates have a direct myocardial depressing effect, decreased tonicity in the musculature of the smaller peripheral vessels with extravasculation of blood. The cardiac and vasomotor centers in the brain are

depressed (Fell et al., 1968; Shubin and Weil, 1971). Typical of severe barbiturate poisoning, especially from barbital, is the development of hypovolemic shock; the hematocrit increases and the blood total protein falls (Moeschlin, 1971). A leukocytosis of as much as 15,000-30,000 white blood cells/mm with a distinct shift to the left often occurs in the absence of infection.

Hypothermia

Hypothermia is due to depression of the temperature regulating mechanism in the pons (Linton and Ledingham, 1966; Upson, 1975).

Gastrointestinal Tract

The effect on the gastrointestinal tract is generally inhibitory and may later be followed by an increase in tone. Further absorption of barbiturate may lead to the cycle repeating itself (Bloomer and Maddock, Jr., 1971).

Genitourinary

The production of albuminuria and hyaline casts in the uremic are the only direct barbiturate effects on the kidney. Other toxic manifestations on the geniturinary system are secondary to shock, hypovolemia, hypothermia, hypotension, and increased secretion of anti-diuretic hormones.

Skin

Cutaneous manifestations of barbiturate hypersensitivity in the form of bullae and blisters are extensively documented (Beveridge, 1971). Their presence is significant in the diagnosis of acute barbiturate intoxication.

Perivascular sloughing as a result of extravascular injection of the strongly alkaline sodium barbiturate salts can be prevented by infiltrating the perivascular tissue with procaine hydrochloride (Elder and Harrison, 1944).

Liver

The most important effect of barbiturates on the liver is their potent stimulation of the enzyme systems that metabolize barbiturates and other chemicals. Enzyme induction associated with increased cytochrome P-450 and other hepatic microsomal drug-metabolizing enzymes has been proposed as an explanation for barbiturate tolerance after repeated dosing in some species (Parke, 1971).

Thrombophlebitis

Deep vein thrombosis and thromboembolization occurs in some patients (Matthew, 1975).

Withdrawal Syndrome

A withdrawal syndrome, though more common in habituated patients, may also occur in those undergoing a first intoxication. Excitement, sleeplessness, dilirium, toxic psychosis and epileptiform fits characterize abstinence during the withdrawal phase (Matthew, 1975).

Fetus

Abortion is rare after severe acute barbiturate poisoning, provided the toxicity has not been complicated by the presence of other poisons and if no severe anoxemia or shock has occurred (Moeschlin, 1971). Barbiturates are contraindicated for cesarean section surgery in veterinary and human medicine (Dreisbach and Synder, 1943).

Electroencephalogram (EEG)

The EEG in a barbiturate-poisoned, comatosed patient shows typical depression. The amplitudes are augmented and the frequency becomes reduced as the severity of poisoning increases (Moeschlin, 1971).

Electrocardiogram (ECG)

The ECG of barbiturate toxicity may reveal pathological findings, such as changes in the Q and T waves with flattening of the T wave or negativity (Moeschlin, 1971).

Cerebrospinal Fluid

Congestion of the central nervous system occurs with barbiturate overdose (Mousel, 1953). Lumbar puncture may be of prognostic value in cases admitted to the clinic some time after ingestion of the drug.

PHYSIOPATHOLOGY

Barbiturates are well absorbed from all sites of administration but their use is not recommended by all routes. The highly alkaline sodium salts are irritating to tissues and only the intravenous route results in a clinical effect with the ultrashort barbiturates.

After absorption, there is good distribution throughout the body, with the highest concentration occurring in the liver, kidney and skeletal muscle. Ultrashort barbiturates are selectively distributed to fat tissue. Barbiturates readily cross the placenta into the fetal blood and pass into milk, though not at levels that will affect the nursing individual (Casarett and Doull, 1975; Dreisbach and Snyder, 1943; Mark, 1971a; Rae, 1962).

The metabolism of barbiturates occurs largely in the liver with

minor metabolism taking place in the kidney. Other tissues that metabolize barbiturates include brain, heart, intestines, muscle, and spleen (Parke, 1971).

The major metabolic pathway for the barbiturates is oxidation, usually at the larger of the two carbon substitutions, producing polar alcohols, phenols, ketones, or carboxylic acids which appear in the urine as free compounds or as pharmacologically inactive glucuronide conjugates. (Casarett and Doull, 1975). The long-acting barbiturates are primarily excreted by the kidneys (thus being contraindicated in renal disease); the short-acting barbiturates are primarily metabolized by the liver (and are contraindicated in hepatic disorders); while the ultrashort-acting barbiturates equilibrate rapidly to fat tissue where they are metabolized or released slowly to be oxidized by the liver and excreted by the kidneys.

The site of action of barbiturates in the brain is not well known but is thought to be somewhere in the cerebral cortex, the thalamus, and/or the reticular activating system (Mark 1971b). The mechanism of barbiturate action is also not completely known. However, barbiturates are said to have an inhibitory effect upon cellular respiration of neurons, while the hypnotic and anesthetic effect are felt to be manifested via influence upon synaptic transmission (Mark; 1971b; Upson, 1975).

DIAGNOSIS OF ACUTE BARBITURATE POISONING

The diagnosis of acute barbiturate intoxication is based on circumstantial evidence and a history of exposure based on interrogations of patients, relatives or owners of animals. Evidence of the clinical signs of intoxication, as previously described, is also helpful. Additional

useful or confirmatory evidence can be obtained from chemical analysis of blood, urine or cerebrospinal fluid and the effects of EEG and ECG.

TREATMENT

In the absence of specific antifotes for barbiturate poisoning, various methods of patient management have been advocated, ranging from simply observing the patient sleep off the effects to a major exercise in resuscitation (Anon, 1951; Bloomer and Maddock, Jr., 1971; Fazekas and Koppanyi, 1958; Honey and Jackson, 1959; Koppanyi and Fazekas, 1952; Mann and Sandberg, 1970; Plum and Swanson, 1957). The basic therapeutic regimen consists broadly of emergency treatment and general care.

Emergency Treatment

The emergency treatment of barbiturate poisoning consists of the managements of respiratory failure and circulatory failure and the prevention of further absorption of the poison and the excretion of that present in the systemic circulation.

Respiratory Failure. Central nervous system stimulants, such as picrotoxin, bemigride, pentylenetetrazole, nikethamide and other analeptics, have been used or advocated to stimulate respiration (Blanchly, 1955; Cole et al., 1960; Eckenhoff and Dam, 1956; Kavelman, 1960; Koppanyi and Fazekas, 1953; Lamere and Brown, 1960; Louw and Sonne, 1956; Nabavro, 1950; Nolan, 1958; Pederson, 1956; Richards, 1959; Thompson, 1958; Worlock, 1956). The harmful effects and futility of analeptics have since been documented, and instead supportive and symptomatic therapy is advocated (Clemmenson and Nilsson, 1951). The merits and disadvantages of analeptics and symptomatic therapy have also

been discussed by Koppanyi and Fazekas (1950, 1952). The current recommended treatment of barbiturate intoxication involves the establishing of a patent airway to provide adequate ventilation and oxygenation. Hypotension, often due to hypoxia and acidosis, may reverse once proper respiratory ventilation is established.

Circulatory Failure. The clinical assessment of peripheral circulatory failure in acute barbiturate poisoning is often difficult since the manifestations of shock are masked by nervous system depression and hypothermia. In the light of what is known of the etiology, elevation of the foot of the bed of affected humans and the use of plasma expanders in all species have been recommended (Lawson and Proudfoot, 1971; Shubin and Weil, 1971) to counter the effects of circulatory failure.

Prevention of Further Absorption. Emesis and gastric lavage have been used to prevent or impede further absorption of barbiturates and thereby significantly reduce morbidity and mortality. Oral administration of activated charcoal adsorbent shortly after barbiturate ingestion is an alternative that is less hazardous but equally effective in preventing the bioavailability of ingested barbiturates (Chin et al., 1970).

Accelerated Excretion of Systemic Barbiturates. In all cases of poisoning, there is already systemic absorption before the patient can receive treatment. Methods of accelerating systemic excretion of the barbiturate then become more important than the use of emetics, lavage, or poison sequestrants. The various methods used to hasten excretion of the absorbed toxicant include urinary alkalinizing agents, forced diuresis, peritoneal dialysis and hemodialysis (Balgot et al., 1961; Bloomer, 1965;

Lassen, 1960).

The use of hemodialysis and peritoneal dialysis for barbiturate intoxication is widely reported in the literature (Berman et al., 1956; Kyle et al., 1953; Lee, 1971; Maher and Schreiner, 1967; Mann and Sandberg, 1970; Rosenbaum et al., 1968; Walsh et al., 1952; Yatzidis, 1971). Exchange blood transfusion is practical in babies and small patients, but it can be risky. The use of ion exchange resins have been investigated and applied to the treatment of barbiturate intoxication (Maher and Schreiner, 1967; Mann and Sanberg, 1970; Pallota and Koppanyi, 1960; Yatzidis, 1971).

Activated charcoal hemoperfusion therapy for severe barbiturate poisoning has also been reported (Chin et al., 1970; Hagstam et al., 1966; Lipscomb and Widdop, 1975; Maher and Schreiner, 1967; Mann and Sandberg, 1970; Rosenbaum, et al., 1968; Widdop et al., 1975; Yatzidis, 1971; Kolthammer, 1976).

General Care

The general care of patients poisoned with barbiturates includes the management of hypothermia, correction of water and electrolyte imbalance, treatment of infection, and general tender-loving-care (Moeschlin, 1971).

Hypothermia. Treatment of hypothermia is controversial due to insufficient data on the precise mechanisms which operate during severe reduction in body temperature.

Water and Electrolyte Balance. Treatment for water and electrolyte balance follow conventional lines of assessment and replacement or maintenance.

Antibiotic Therapy. When there is clinical and laboratory support for the diagnosis of infection in barbiturate-poisoned patients, a suitable antibiotic should be given without delay. There is considerable controversy about the use of prophylactic antibiotics in patients unconscious from barbiturate poisoning (Matthew, 1975).

Nursing Care. Good nursing care of a high standard is essential for patient survival, regardless of which regimen of treatment is instituted. Such care includes turning of the patient half-hourly to avoid occurrence of skin pressure sores, passive movement of the limbs with percussion of the chest, maintenance of the patency of airways, and the protection of the eyes by instilling methyl cellulose drops into the conjuctival sac and taping the eyelids to prevent exposure keratitis (Lawson and Proudfoot, 1971).

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APPENDIX C

ETHYLENE GLYCOL TOXICOSIS AND THERAPY

A LITERATURE REVIEW

ETHYLENE GLYCOL TOXICOSIS AND THERAPY

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SYNONYMS

Ethylene glycol (EG), chemical formula CH_2OHCH_2OH, is also known as ethylene alcohol, glycol, and 1-2-ethane-diol, and by various trade names (Hawley, 1971).

CHEMISTRY

Ethylene glycol is a clear, colorless, syrupy liquid that is bitter-sweet tasting and hygroscopic. It is relatively non volatile and is miscible with water, aliphatic alcohols, aldehydes and ketones. The specific gravity is 1.1155 (20°C), the boiling point is 197.2°C, the freezing point is 13.5°C, and it has a refractive index of 1.430 at 25°C. The chemical is combustible and undergoes autoignition at a temperature of 775°F (413°C).

Ethylene glycol is prepared: by heating ethylene chlorohydrin with a solution of an alkali carbonate or bicarbonate; by oxidation of ethylene with air, followed by hydration of the oxide formed; and from formaldehyde, water and carbon monoxide, with hydrogenation of the resulting glycolic acid (Browning, 1965; Hawley, 1971; Merck and Company, 1968; Polson and Tattersall, 1969; Rowe, 1967; Widman, 1946).

USES

Ethylene glycol's capacity for lowering the freezing point of water has been exploited for its use as an antifreeze in automobiles. It is also used as a circulant coolant of automobiles and lunar modules and as a heat-

transferring agent in refrigeration and electron tubes (McChesney et al., 1971; and Hawley, 1971). As a solvent, it is intermediate between glycerine on one hand and alcohol and acetone on the other. Ethylene glycol is used as a solvent in the paint, plastic and pharmaceutical industries, as well as in the synthesis of safety explosives (Hawley, 1971; Merck and Company, 1968).

Ethylene glycol has been used as a preservative for fruit, juices and alcohol-free drinks and has been used medically as a substitute for glycerine (Widman, 1946). The internal use of EG is banned in the USA, and a topical concentration of over 5% has been considered a health hazard (Gleason et al., 1969; Polson and Tattersall, 1969).

TOXICITY

Man

Ethylene glycol appears to be more toxic to man (MLD 1.6 g/kg body weight) than to laboratory animals (Gessner et al., 1961). Human poisoning has resulted primarily from its accidental ingestion as a substitute for alcoholic beverages (Berman et al., 1957; Bove, 1966; Miles, 1946; Moriarty and McDonald, 1974; Pons and Custer, 1946; Smith, 1951; Widman, 1946; Wills et al., 1974).

The route of exposure is usually po, but skin and eye contact may occur in industry. The minimum allowable concentration of EG in the environment has not been established (Browning, 1965; Merck and Company, 1968; Polson, 1969; Rowe, 1967), although there is little inhalation risk owing to its low volatility at ordinary temperatures and its irritant nature. The result of human exposure to aerosolized EG for 4 weeks was negative, and no evidence was found that a tolerable concentration

for a 4 week uninterrupted exposure had any deleterious effect on the psychological or other functions of the body (Wills, 1974).

Animals

Accidental poisoning has been reported in dogs (Berg, et al., 1971; Jacobson, 1951; Jonsson and Rubarth, 1967; Kersting and Nielsen, 1951), cats (Hadlow, 1957; Jonsson and Rubarth, 1967; Kersting and Nielson, 1965), poultry (Riddel et al., 1967), swine (Osweiler and Eness, 1972), and rabbits (Page, 1926).

Monkeys. The lethal oral LD_{50} for monkeys is less than 2.5 ml EG/kg body weight (Peterson et al., 1964). The toxic dose for Maccaca mulata and M. irus is probably similar to that for man.

Dogs. The oral administration of 4.2 and 4.4 ml EG/kg body weight was fatal for dogs (Beckett and Shields, 1971; Jonsson and Rubarth, 1967). An oral minimum lethal dose of 6.6 ml EG/kg body weight was reported by Kersting and Nielsen (1966), although some dogs required as much as 13.2 ml EG/kg body weight. This variation was attributed to individual idiosyncratic variations in some of the dogs. Sanyer et al. (1973) reported fatalities in untreated dogs receiving EG orally at dose levels of 10, 8, or 6 ml/kg of body weight.

Cats. The minimum oral lethal dose of EG for cats has been estimated to be 1.5 ml/kg body weight (Merck and Company, 1968). However, doses of 2 g EG/kg body weight (Spector, 1956) and 1 g EG/kg body weight (Gessner et al., 1961) have been reported to cause fatalities in cats. Miles (1946) observed recovery in a cat receiving 1 ml EG/kg body weight. Ethylene glycol orally administered to cats at dose levels of 4, 6 or 8

ml/kg of body weight was also reported to be fatal (Penumarthy and Oehme, 1975). The sensitivity of cats to EG was explained on the basis that cats form more oxalic acid than other species (Gessner et al., 1961; Park, 1968).

Poultry. The median lethal dose of EG to poultry was estimated to be 67.5 ml/l of drinking water. Birds receiving 25 ml or more of EG/l had oxalate crystals in their renal tubules (Riddel et al., 1967).

Chronic Toxicity

Chronic toxicity studies with EG have been conducted in monkeys and dogs.

Monkeys. Blood et al. (1962) observed no toxic effects in the Rhesus monkey when EG was given as 0.2% and 0.5% of the diet over a 3-year period. During the administration of 0.25-10% EG in the drinking water of several Maccaca species, Roberts and Seibold (1969) reported calcium oxalate crystals within the kidney proximal tubules, and tubular degeneration resulted from doses of 15 ml EG or more/kg body weight.

Dogs. A dog was given 1,036 ml of EG over 6 months time without ill effects (Kersting and Nielsen, 1966).

CLINICAL SIGNS

The clinical signs of EG poisoning have been reported for humans and domestic animals (Beckett and Shields, 1971; Browning, 1965; Flanagan and Libcke, 1964; Friedman et al., 1962; Gleason et al., 1969; Hadlow, 1957; Jonsson and Rubarth, 1967; Kersting and Nielsen, 1965 and 1966; Miles, 1946; Moriarty and McDonald, Jr., 1974; Oehme, 1974; Osweiler, 1969; Polson

and Tattersall, 1969; Pons and Custer, 1946; Sanyer et al., 1973; Wacker, 1971; Wacker et al., 1965; Wills et al., 1974). The clinical course is usually divided into three stages.

Stage I

This is essentially a central nervous system involvement which develops ½-1 hr after EG ingestion. Nausea, vomiting, signs akin to ethanol intoxication, somnolence, occasional diarrhea, ataxia, increased abnormal reflexes, abdominal pain, subnormal temperature, polyuria, hematuria, proteinuria, and crystalluria may be observed. This stage progresses into acidosis, paralysis, and coma within 4-6 hr if high doses of EG are involved. The patient is usually presented to the veterinary clinic at this state. Convulsions may develop at the later part of this stage, and death can follow.

Stage II

The second stage is characterized by cardiopulmonary signs. Hyperpnea, tachycardia and moderate tachypnea are the early constant findings. Bradycardia is seen in the terminal stages of fatal poisoning. The patient may remain comatosed for 2-12 hr. Death usually occurs 8-36 hr post-ingestion and results from pulmonary edema and/or cardiac failure.

Stage III

For patients surviving stages I and II, the final phase is renal failure due to the accumulation of oxalate crystals in the renal tubules. Anuria, uremia, coma and death may occur 5-14 days after the initial EG ingestion.

POST MORTEM LESIONS

The primary gross post mortem lesion of EG acute poisoning is congestion of all body tissues. Generalized edema in humans (Pons and Custer, 1946), pulmonary edema, swollen kidneys, and hyperemia of the gastrointestinal mucosa and brain have been observed. In a subacute or delayed death, dehydration, uremic ulcers of the buccal cavity, and hemorrhagic gastritis are characteristic lesions (Kersting and Nielsen, 1966; Roberts and Seibold, 1969; Sanyer et al., 1973).

The histologic lesions are confined to the kidneys. Biregringent crystals of light yellow color are found primarily in the proximal convoluted tubules. Histochemical examination and differential staining has identified the crystals as salts of oxalic acid, principally calcium oxalate (Beckett and Shields, 1971; Jacobson, 1951). When seen under polarized light the crystals appear brilliant and doubly refractile (Jacobson, 1951; Kersting and Nielsen, 1966). The renal deposition of large numbers of oxalate crystals is pathognomonic for EG poisoning in small animals (Beckett and Shields, 1971; Jacobson, 1951; Kersting and Nielsen, 1965; Kersting and Nielsen, 1966). In humans, however, the same observation can be due to primary oxalosis, a congenital disease of childhood due to faulty metabolism of glycine. Other kidney histologic findings of EG poisoning are hydropic degeneration, cystic tubules, and acidophilic casts.

The lungs are edematous and hyperemic as a result of the direct early toxic effects of EG (Friedman et al., 1962).

The central nervous system lesions include hyperemia of the brain, focal loss of Purkinge fibers (Friedman et al., 1962; Roberts and Seibold, 1969), acute encephalitis and meningitis (Pons and Custer, 1946), and small crystal deposition in the blood vessels of the brains of humans, dogs,

monkeys, and rats (Friedman et al., 1962; Jonsson and Rubarth, 1967; Kersting and Nielsen, 1966; Roberts and Seibold, 1969; Smith, 1951).

The liver is distented with blood (Friedman et al., 1962; Jonsson and Rubarth, 1967; Kersting and Nielsen, 1965; Kersting and Nielsen, 1966; Roberts and Seibold, 1969) and central hydropic degeneration is seen. Hepatic fatty changes with focal necrosis occur in humans (Friedman et al., 1962; Pons and Custer, 1946), and moderate liver edema with centrolobular hemorrhage is observed in dogs (Kersting and Nielsen, 1966).

The gastrointestinal mucosa is hyperemic as a result of the direct toxic effect of EG on the endothelial cells (Kersting and Nielsen, 1965).

Cardiac enlargement and myocarditis in humans (Friedman et al., 1962), and concentric dilation of the heart in cats (Miles, 1946), have also been reported.

Human skeletal muscle has shown interstitial myositis (Friedman et al., 1962) which has not been observed in domestic animals.

PATHOGENESIS

The mechanism of EG toxicity is not yet completely understood. However, species variation in the biotransformation of the compound is reflected in the variation of sensitivity of the various animals to the chemical.

EG is readily absorbed after oral ingestion and is uniformly and rapidly distributed throughout the blood and body tissues (Backman and Goldberg, 1971). Maximum EG blood concentration occurs 3-4 hr after oral administration to dogs (Nunamaker et al., 1971; Sanyer et al., 1973).

Rat liver preparations containing liver alcohol dehydrogenase oxidized EG to oxalic acid (Williams, 1959). Other studies have shown intermediate metabolites from the biotransformation of EG (Gessner et al.,

1960; Gessner et al., 1961; Park, 1968; Peterson et al., 1964; Von Wartburg et al., 1962; Williams, 1959). The complete series of EG metabolites include glycoaldehyde, glycolic acid, and glyoxylic acid (Gessner et al., 1960; Gessner et al., 1961). Glyoxylic acid is then degraded into principally formic acid and carbon dioxide with glycine and oxalic acid formation as minor end products.

The major excretory products are respiratory carbon dioxide and unchanged urinary EG. Glomerular filtration and passive reabsorption are the mechanism for urinary excretion of EG (Swanson and Thompson, 1969).

The pathogenesis of clinical intoxication probably follows sequential effects from the initial high EG blood concentration, the developing acidosis due to the intermediaries and metabolites, and the progressive uremia caused by renal oxalate deposition.

SPECIES BIOTRANSFORMATION VARIATIONS

Ethylene glycol is most toxic to species that excrete primarily oxalate salts and unchanged EG in the urine, and is least toxic to species which oxidize EG to carbon dioxide.

Rabbits, Rats and Monkeys

At low doses of ^{14}C-labelled EG (0.1-2.0 g/kg), rabbits and rats excreted 17-28% of the activity unchanged in urine and 60% as carbon dioxide in expired air. At doses of 2.5 and 5 g/kg, nearly 50% of the radioactivity was recovered in the urine. The oxalic acid output was not more than 0.27%. It was concluded that EG toxicity is partly due to the unchanged glycol (Friedman et al., 1962; Gessner et al., 1961; Miles, 1946; Wacker et al., 1965).

The amount of EG converted to oxalic acid varies with the species

(Gessner et al., 1961; Parke, 1968). In man this is less than 2%; in rabbits more than 0.37%; in guinea pigs less than 0.5%; and in cats 0.7-3.7%. Of the species mentioned, the toxicity of EG is highest in cats.

Glycolic acid is the most important urinary metabolite in monkeys and rats, after carbon dioxide and unchanged EG. The oxalic acid output is about 0.3% in monkeys and 2.5% in rats. Monkeys excreted 0.1% of the EG as hippuric acid. A glucuronic acid conjugate of EG has not been found in humans or animals (Gessner et al., 1960).

The administration of glycolaldehyde, glycolic acid, and glyoxylic acid to rats resulted in renal tubular oxalosis (Bove, 1966), thus supporting the sequential degradation of EG proposed by Gessner et al. (1961). Each of the three compounds used was more toxic than the parent EG. Studeis in partially hepatectomized rats (Richardson, 1973) showed glyoxylate to be more toxic than EG or glycolate. Partial hepatectomy increased the urinary concentration of oxalates in rats fed glyoxylate, but not in rats fed EG, glycine, or glycolate. Progressively increasing oxalate synthesis followed glycine, EG, glycolate, and glyoxylate administration; hence the suggestion that the toxicity of EG is primarily due to the glyoxylate and oxalate metabolites.

THE SUBCELLULAR EFFECTS OF ETHYLENE GLYCOL

The subcellular effects of the major EG metabolites have been studied in mitochondria from liver, kidney and brain of dogs, rats and monkeys (Bachman and Goldberg, 1971). Tissue respiration, oxidative phosphorylation, and citric acid activites were unaffected by EG, but substrate-level phosphorylation was inhibited at 10 mM and higher concentrations. However 1 mM or higher concentrations of glyoxylic acid showed reduced mitochondrial respiration and uncoupling of oxidative

phosphorylation. Glyoxylate at 10 mM or higher concentrations also inhibited the citric acid cycle enzymes (isocitrate and alpha-ketoglutarate dehydrogenase). At low levels of exposure, the adverse effects of EG are most likely due to the formation of glyoxylate which interacts with such citric acid intermediates as oxaloacetate.

PROPOSED TREATMENTS

For many years the treatment of EG poisoning centered around the treatment of the oxalic acid formation (Miles, 1946). Induction of emesis, gastric lavage, and calcium therapy were used (Browning, 1965; Gleason et al., 1969; Sanyer et al., 1973). The lack of success with this mode of therapy has been ascribed to the short course of the poisoning and the variable length of time between ingestion and initiation of treatment. Early attempts at treatment in animals were mostly supportive and death was the usual result (Browning, 1965; Jacobson, 1951).

Peritoneal dialysis was used for EG toxicosis to reduce both blood and tissue levels of the toxicant and its metabolites and to correct the resulting acidosis. Some recoveries were reported with this therapy after the ingestion of lethal doses of EG and following several days of oliguria and coma (Flanagan and Libcke, 1964; Friedman et al., 1962; Smith, 1965).

The use of ethanol as an antidote resulted from studies of the biochemical properties of the liver enzyme alcohol dehydrogenase (Gessner et al., 1961; Krebs and Perkins, 1970; Levy, 1960; Von Wartburg et al., 1964). Peterson et al. (1964) found the LD_{50} of EG for rats treated with ethanol to be twice that of untreated rats. Squirrel monkeys (Saimiri sciurea) given toxic doses of EG died, while those monkeys receiving ethanol within 30 minutes after the EG dose survived. Animals given EG and

ethanol in combination excreted 75% of the administered EG unchanged in the urine, while those given EG alone excreted less than 10% of the dose as unchanged EG and developed oxaluria.

Two men severely poisoned by EG were successfully treated with a combination of ethanol and sodium bicarbonate to correct the acidosis and with repeated peritoneal dialysis (Wacker et al., 1965).

Borden (1968) tested the value of alkalinizing agents such as sodium bicarbonate in the treatment of EG toxicity. Although ethanol and sodium bicarbonate each individually reduced the toxicity of EG in rats, the highest survival rate and least tissue toxicity occurred when ethanol and sodium bicarbonate were given together. Sodium bicarbonate increased the amount of urinary citrate concentration and produced urinary alkalosis, thus enhancing citrate-calcium combination and reducing the amount of calcium available for combination with oxalate (Beckett and Shields, 1971; Borden, 1968).

Penumarthy and Oehme (1975) used ethanol and sodium bicarbonate in isotonic saline solutions to cats poisoned with EG. Treatment was successful for the EG dose of 6 ml/kg; however, recovery related to the dose of EG administered and the time interval between poisoning and the initiation of therapy. Other successful experiments with EG-poisoned dogs and treatment with ethanol and sodium bicarbonate ip (Beckett and Shields, 1971), ethanol iv (Nunamaker, 1971), and ethanol iv followed by sodium bicarbonate ip (Sanyer et al., 1973) have been reported.

An allogenic renal transplant was tried in one instance of a dog poisoned with EG (Berg et al., 1971). The patient died from a generalized mycotic infection 11 days after surgery.

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APPENDIX D

SODIUM FLUORIDE TOXICOSIS AND THERAPY

A LITERATURE REVIEW

SODIUM FLUORIDE TOXICOSIS AND THERAPY

A LITERATURE REVIEW

INTRODUCTION

Fluoride (F) is an essential element in the human or animal body. There is no evidence to indicate that F deficiency is an important problem in domestic animals (Smith et al., 1972); however, excessive intake of F may lead to acute and/or chronic toxicoses in man and animals. Fluoride is normally present as 0.01-0.02% of the enamel of teeth, and 0.01-0.03% of bones is F (Kerur, 1971).

Poisoning from both organic and inorganic F compounds is a clinically recognized entity. Organic fluoride toxicosis in man and animals is due to the ingestion of sodium monofluoroacetate (1080) rodenticide or plants containing fluoroacetic acid; viz. Dichapetalum spp. in Africa, Acacia geoginae and Gastrolobium grandiflorum in Australia, and Palicourea marcgravi in Brazil (Egyed, 1971; Atzert, 1971; Peters, 1973). Inorganic fluoride toxicity, the focus of this writing, can cause chronic fluorosis in man and animals and produces occasional acute toxicosis as well.

PHYSICAL AND CHEMICAL PROPERTIES

Sodium fluoride (NaF) occurs as clear, lustrous crystals or a white powder. It is soluble in water and only slightly soluble in alcohol. The specific gravity is 2.558 (at 41°C), the melting point is 988°C, and the boiling point 1695°C. It is derived by adding sodium carbonate to hydrofluoric acid (Hawley, 1971).

USES

Fluoride is added to water supplies because of its anticariogenic properties. It is used as an insecticide (not on living plants) and as a fungicide and rodenticide. It finds uses in industries for the treatment of steel, in wood preservatives, for chemical cleaning and electroplating, in the manufacture of glass, as a vitreous enamel and a preservative for adhesives, in toothpastes, and as single crystals used as windows in ultraviolet and infrared detecting systems (Hawley, 1971).

TOXICITY

Sodium fluoride is highly toxic by ingestion and inhalation, 2.5 mg/m^3 of air (as F) being the tolerance level. The minimum amount of F, in the form of soluble fluoride, required to produce toxicity in farm animals lies between 1 and 2 mg/kg body weight per day or 12-27 ppm of the diet (Smith et al., 1972). However, Runnels et al. (1965) claimed 100 ppm (0.07%) is the maximum safe amount of F for the dry ration of cattle, sheep, and pigs; 350 ppm may be allowed in the rations of poultry.

Acute Toxicity

Acute inorganic fluoride toxicosis in animals can result from sodium fluoride being used for the control of ectoparasites and endoparasites in swine and poultry (Runnels et al., 1965; Smith et al., 1972).

In humans, acute fluoride toxicity has resulted from the accidental ingestion of sodium fluoride mistaken for sugar, salt or baking soda. Problems have also followed the ingestion of laundry powder and the ingestion of roach powder, all of which contain sodium fluoride (Yolken, 1976, Abukurah, 1972).

Chronic Toxicity

Chronic fluorosis has been described in cattle (Jones, 1972a, b; Hemingway and Weaver, 1972), in horses (Shupe and Olson, 1971), and as "slobbers" of guinea pigs in Australia (Hard and Atkinson, 1967; Parsonson et al., 1975).

Some of the sources that contribute to excessive chronic ingestion of fluorides are forages in areas near certain industrial plants subjected to airborne contamination, drinking water high in fluoride content, feed supplements, mineral mixtures high in fluoride content, and vegetation growing on soils high in fluoride content (Shupe et al., 1963; Shupe and Olson, 1971; Jones, 1972a).

In humans, chronic fluorosis is endemic and an occupational disease in persons engaged in or living near industrial plants utilizing fluoride compounds (Bond and Murray, 1951; Krishnamachari and Krishnaswamy, 1973; Marier, 1968). The ingestion of 320 mg sodium fluoride/day for periods of 5-6 months has not resulted in evidence of acute or chronic toxicity in man (Black et al., 1949). Taves (1971) identified organic fluorine in human but not in animal serum.

CLINICAL SIGNS

Acute

The clinical signs of acute human inorganic fluoride toxicosis have been documented (Abukurah et al., 1972; Berman et al., 1973; Yolken, 1976). Clinical signs and laboratory experimental observations include bloody mucoid gastric secretions, tetany, ventricular fibrillation and arrhythmias, esophageal stricture, severe hypocalcemia, mild hypotension, prolonged QT intervals, and respiratory failure.

The clinical signs observed in experimentally poisoned rats include ataxia, muscle weakness, central nervous system depression, and occasional muscle tremors (Conine et al., 1975).

Chronic

Chronic fluorosis has been documented in man (Cook, 1971; Krishnamachari and Krishnaswamy, 1973; Marier, 1968). Symptoms include crippling deformities of the skeleton due to kyphosis, stiffness of the spine, reduced mobility of bony cage, and bony exostoses. Human skin lesions due to chronic fluorosis are described (Marier, 1968).

The symptoms of chronic fluorosis have been extensively documented in animals (Jones, 1972a, b; Newell and Schmidt, 1958; Rand and Schmidt, 1952; Schmidt et al. 1954; Schmidt and Rand; Shupe and Olson, 1971; Shupe et al., 1962; Shupe et al., 1963; Sultie, et al., 1971; Weatherell and Weidmann, 1959; Weatherell, 1959; Zipkin et al., 1964). The most prominent clinical signs include mottling and abrasion of teeth, intermittent lameness, and periosteal hyperostosis. More than 6 ppm F is usually found in urine.

The pathognomonic lesions of chronic F poisoning involve the teeth, bone and kidneys. The principal changes are in the teeth, bone and kidneys. The principal changes in the teeth are "chalky" areas, mottling, excessive attrition, and hypoplastic pitting of the enamel. Marked polydipsia and polyuria, with low specific gravity of the urine, are observed.

Other lesions associated with chronic fluorosis are hoof abnormalities, chronic diarrhea, loss of condition, decreased milk production, and occasional abortion (Oehme, 1975).

In guinea pigs, the older animals are primarily affected. Marked

weight loss leading to emaciation, a rough hair coat, and a reluctance to move, with affected animals often sitting hunched in a corner of the cage, are observed. There may be decreased food intake, polydipsia and, later, the "slobbers" condition. Abortion and stillbirths were observed at this latter stage (Parsonson et al., 1975).

DIAGNOSIS

Diagnosis is based on history of circumstantial evidence of exposure, physical examination of the patients, some or all of the clinical signs, and the F content in suspected materials or spinal biopsies (Suttie, 1967).

PHYSIOPATHOLOGY

Despite the long-time recognition of acute and chronic F poisoning, there is still uncertainty of the relative importance of several F actions in causing death. These known effects include interference with the parathyroid gland (Faccini and Care, 1965) and calcium utilization, inhibition of enzymes, induction of shock, electrolyte imbalance due to fluid loss from vomiting and diarrhea, and vascular or respiratory depression (DeLopez et al., 1976). Plasma F concentration is dependent upon the degree of F absorption from the gastrointestinal tract and removal of F from the blood by the skeletal system and kidneys. Marier (1968) discussed in terms of bone and serum manifestations the interrelation of F with calcium, phosphorus, citrate, alkaline phosphatase, the parathyroid hormone, and vitamin D in rats.

Fluoride enters more readily into biologically active tissue than into static bone (Weidmann and Weatherell, 1959). It appears to depress osteoblasts and concomitantly stimulates osteoclasts, even though both

cells contain acid phosphatase which is known to be inhibited by F *in vitro* (Faccini and Care, 1965).

The mechanism of the anticariogenic effect of F is still unknown. A F-induced reduction in the solubility of surface tooth enamel apatite is a likely explanation (Marier, 1968).

TREATMENT

No effective antidote is available for acute F toxicosis. Some clinicians manage acute F poisoning with gastric lavage, intravenous calcium gluconate, emergency resuscitative measures (Abukurah *et al.*, 1972), peritoneal dialysis (Yolken, 1976), or hemodialysis (Berman *et al.*, 1973). Further research is needed of effective methods to manage acute F poisoning.

There is no effective treatment of chronic fluorosis. However, the addition of aluminum to the diet reduces the absorption of F from the digestive tract (Oehme, 1975). Massive amounts of vitamin C in the diet had no effect (Krishnamachari and Laxmaiah, 1975).

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APPENDIX E

DETOXIFICATION OF POISONS WITH ACTIVATED CHARCOAL

A LITERATURE REVIEW

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SYNONYMS

Medicinal carbon, active carbon (Osol and Pratt, 1975).

DESCRIPTION

Activated charcoal (AC), a general-purpose antidote and a pharmaceutical aid (adsorbent), is a fine, black, odorless, tasteless powder free from gritty matter (Osol and Pratt, 1975; USP, 1975). The surface area of 1 ml of finely divided AC is approximately 1000 m^2. The properties which enhance the adsorptive efficacy of AC include its small particle size, large surface area, and low content of adsorbed substances (Osol and Pratt, 1975).

PREPARATION

Activated charcoal is obtained as residue from the destructive distillation of various organic materials that are treated to increase its adsorptive power. It may be derived from wood, bone, blood, rice, starch, coconut pericarp, and industrial wastes, such as wood pulp, paper and molasses.

The activation may be achieved by treating the charcoal at high temperature with steam, carbon dioxide, or dehydrating substances, such as sulphuric acid, phosphoric acid or zinc chloride, or by any combination of the above methods. If the charcoal is to be used for medicinal purposes it is thoroughly washed to remove any inorganic matter that may be present (Osol and Pratt, 1975).

USES

Activated charcoal has found uses as a decolorizer and as an adsorbent of impurities from organic and inorganic compounds in the manufacturing and pharmaceutical industries (Anon., 1974; Dunea and Kolff, 1965; Goodman and Gilman, 1970).

Activated charcoal is used in the refining of sugar; in the manufacture of respirators, industrial and war gas masks; to freshen air in submarines and space crafts; to mellow the taste of bourbons; and as filters of water and cigarettes (Anon., 1976; Dunea and Kolff, 1965).

In medicine, AC has been used with limited success to effect the elimination of drug residues in tissues of food animals (Braund et al., 1970, Crookshank et al., 1972; Fries et al., 1970), to adsorb gaseous products of fermentation in dyspepsia and flatulence, to treat diarrhea and dysentery of chronic ulcerative colitis and similar conditions, and as a dressing for suppurating gangrenous wounds (Goodman and Gilman, 1970; Osol and Pratt, 1975).

ABSORPTIVE CAPACITY

The use of AC as an emergency antidote for the treatment of ingested poisons has been advocated for over two centuries. Holt and Holz (1963) concluded that AC has a wide spectrum of activity and that, when properly used, it is probably the most valuable single antidotal agent in our possession. Other writers have reviewed and updated the adsorptive spectrum of AC (Corby et al., 1970; Corby and Decker, 1974; Mann and Sandberg, 1970; Picchionni, 1970).

Dedrick et al. (1967) and Winchester et al. (1974) have worked on

the kinetics of the activated carbon kidney machine and hemoperfusion. The adsorptive capacity of AC depends on many factors, among which are the specific chemical structure of the toxicant as well as the milieu in which the poison is found (Chin et al., 1970; Corby and Decker, 1974; Picchionni, 1970).

It is known that many endogenous and exogenous poisons, including organic, inorganic and metallic compounds, are adsorbed at varying degrees to AC (Chernish, 1972; Corby et al., 1970; Corby and Decker, 1974; Holt and Holz, 1963; Mann and Sandberg, 1970; Picchionni, 1970). Some of the compounds adsorbed by AC are shown in Tables E1, E2, and E3.

THE USE OF ACTIVATED CHARCOAL TO PREVENT SYSTEMIC ADSORPTION OF POISONS

The methods of treating ingested poisons which have no specific antidotes, aside from symptomatic and general supportive therapy, are of two types: those aimed at minimizing absorption by terminating the toxic exposure and those designed to promote the excretion of the already absorbed poisons (Gosselin and Smith, 1966).

The induction of emesis, the application of gastric lavage and enemas, the administration of laxative and cathartics, and the ingestion of adsorbents have been used to limit or prevent the bioavailability of toxicants present in the gastrointestinal tract.

In order to promote the excretion of absorbed poisons, many techniques for accelerating renal and bilary excretion, including extracorporeal hemodialysis, peritoneal dialysis, gastric dialysis, and hemoperfusion, have been used (Lampe, 1975; Maher and Shreiner, 1967; Okonek and Hofmann, 1975; Phansalkar and Holt, 1968; Rosenbaum, 1972).

Studies have shown that gastric lavage and pharmacologic emetics

(apomorphine and syrup of ipecac) are unreliable in effecting stomach emptying of poisons and in addition present hazards from trauma during the lavaging process (Decker et al., 1968; Decker, 1971; Fane and Decker, 1970; Fane et al., 1971; Leading Article, 1972; Phansalkar and Holt, 1968). A safe and equally effective alternative is the oral administration of AC (Belz, 1974; Belz and Bader, 1974; Chin et al., 1970; Comstock, 1971; Corby and Decker, 1968; 1974; Crammer and Davies, 1972; Decker et al., 1968a; Decker et al., 1968b; Dordoni and Wilson, 1973; Fane and Decker, 1970; Ferguson, 1970; Furr and Carson, 1975; Gazzard et al., 1974; Hartel et al., 1973; Hayden and Comstock, 1975; Holt and Holz, 1963; Levy and Gwilt, 1972; Levy and Tsuchiya, 1972; Lipscomb and Widdop, 1975; Matthew, 1972; Phansalkar and Holt, 1968; Scherz, 1974; Sparks et al., 1971; Tsuchiya and Levy, 1972a, b).

Some of the factors that need clarification for the effective and acceptable use of AC are the choice of antidote, the amount and dosage form of the AC, stability of the AC-poison complex, timing of treatment, and frequency of treatment (Chin et al., 1970; Corby and Decker, 1974; Dordoni et al., 1973; Phansalkar and Holt, 1968; Picchionni, 1970).

Choice of Antidote

The importance of prudent selection of the most effective commercial charcoal preparation cannot be overemphasized. Charcoals, though similar in gross appearance, may possess as much as fifty-fold variations in their adsorptive properties; other preparations are virtually useless (Holt and Holz, 1963). The so-called "universal antidote" (2 parts of AC, 1 part of magnesium oxide, and 1 part of tannic acid) or burnt toast have been shown to be less effective than activated charcoal alone (Picchionni et al., 1966).

Picchionni et al. (1974) assessed the relative antidotal efficacy of four brands of AC and found that Activated Charcoal-Merck (Merck Co., Inc., Rahway, New Jersey), Nuchar C (West Virginia Pulp and Paper Co., New York), and Norit A (American Norit Co., Inc., Jacksonville, Florida) displayed similar adsorptive capacity for aspirin and chlorpheniramine. Darco G-60 (Atlas Chemical Co., Wilmington, Delaware) was approximately 35% less effective than the other three AC brands.

Amount and Dosage Form

The use of inadequate quantities of AC has carried over to clinical practices, possibly as the result of extrapolation from in vitro experiments with AC carried out under idealized conditions. Two reference books much used by physicians recommend a dose of 10 g, with a range of 5-50 g (Osol and Pratt; USP, 1975). Others suggest an optimal charcoal-drug ratio of 8:1 (Picchionni et al., 1974).

It is known that the larger the amount of AC used the better the result in countering the opposing effects of gastrointestinal tract motility, digestive secretions, food in stomach, chemical insolubility of the toxicant, pH, and enterohepatic circulation of the poison in the gastrointestinal tract. The ideal dose of AC to adsorb toxicants in gastrointestinal tract is in the range of 100-120 g (Comstock, 1971; Comstock, 1975; Goodman and Gilman, 1970; Hayden and Comstock, 1975).

The current recommendation for humans is to suspend 100 g of dry AC in six ounces (180 ml) of water to form a slurry. The dose is administered through a lavage tube or by voluntary ingestion if the patient is conscious.

The use of AC in tablet form, thickened with agents like sodium carboxymethyl cellulose, sodium alginate, carrageenan, bentonite, gelatine, clay, polysaccharide, or flavored with fruit extract or chocolate has been

practiced but is condemned (Gazzard et al., 1974; Hayden and Comstock, 1975; Levy and Gwilt, 1972; Manes and Mann, 1974; Tsuchiya and Levy, 1972).

pH and Charcoal-Poison Stability

The possibility of poison elution from AC in the gastrointestinal tract due to such factors as pH changes, digestive juices, bile, and food particles has been suggested. However, the deadsorptive effect is little or non-existent in vivo (Picchionni, 1970) and may be offset by the large dose of antidote administered.

Time of Treatment

The longer the time interval between ingestion of the poison and the initiation of AC antidotal therapy, the less effective is the resultant sequestration of gastrointestinal poison. This is due to the greater potential for systemic absorption to have taken place.

The safe interval between poison ingestion and effective AC administration is determined by the rate of absorption of the poison from the gastrointestinal tract. A 30-minute delay is generally considered acceptable. However, some beneficial postsystemic absorptive effect can be obtained by later AC therapy in poisoning caused by drugs which undergo enterohepatic circulation (Belz, 1974; Belz and Bader, 1976; Crammer and Davies, 1972; Hartel et al., 1974; Leading Article, 1972; Rauws and Van Noordwjk, 1972).

Repeated Activated Charcoal Treatment

After an initial adequate dosing with AC, repeated treatment produces no additional inhibition of poison absorption. Additional AC treatment, however, may be useful in reducing tissue levels of poisons that

undergo enterohepatic circulation (Belz, 1974; Belz and Bader, 1974).

THE USE OF ACTIVATED CHARCOAL TO ENHANCE SYSTEMIC EXCRETION OF POISONS

In most instances of poisoning arising from ingestion, there is significant systemic absorption of the toxicant before oral AC therapy can be instituted. The route of exposure may also be pulmonary or topical. If these poisons do not undergo enterohepatic circulation, AC treatment is of no value.

An important type of intoxication is endogenous poisoning secondarily to primary or organic diseases, such as in chronic kidney failure and acute or chronic liver failure. Oral AC therapy is not of value in these cases of poisoning.

When there is systemic intoxication, efforts are directed towards enhancing excretion of the exogenous and endogenous poisons. The use of hemodialysis (Kyle et al., 1953; Maher and Schreiner, 1967), ion exchange resins (Pallota and Koppanyi, 1952; Rosenbaum, 1972), and AC hemoperfusion have gained acceptance as procedures offering the most promise in this direction (Yatzidis, 1971).

The use of AC hemoperfusion is the result of intensive investigations conducted by Yatzidis (1964, 1971, 1972) between 1961 and 1964. He demonstrated that AC in vitro can adsorb considerable amounts of urea, creatinine, uric acid, phenols, indican, guaridines, organic acids, barbiturates, salicylates, and gluthemide from plasma and gastrointestinal juices. This preliminary work was followed by the use of AC in oral and hemoperfusion therapy for chronic renal insufficiency (Yatzidis, 1964; 1971) and subsequently extended to the management of exogenous poisoning (DeMythenaere et al., 1967; Dunea and Kolff, 1965; Hagstam et al., 1966;

Yatzidis et al., 1965; Kolthammer et al., 1976).

Activated charcoal hemoperfusion has now been used to treat poisoning resulting from organic disease, like chronic renal insufficiency (Amdahl, 1975; Chang and Malave, 1970; Chang et al., 1971; Chang et al., 1972; Chang et al., 1974; Dedrick et al., 1967; Yoshida and Okazaki, 1974), acute and chronic liver failures (Anon, 1976; Gazzard et al., 1974; Weston et al., 1974), and intoxication from numerous exogenous compounds (Andrade et al., 1972; Brookings and Ramsey, 1975; Carvallo et al., 1976; Davis et al., 1974; DeMythenacre, 1967; Gazzard et al., 1974; Hagstam et al., 1966; Hartel et al., 1973; Horres et al., 1976; Rosenbaum et al., 1968; Widdop et al., 1975; Wilson et al., 1973). Hemoperfusion chemotherapy for sickle-cell anemia has also been proposed (Kjellstrand et al., 1974).

TOXICITY AND SIDE EFFECTS

Nau et al. (1958a, b, 1962) have studied the toxicity of AC by ingestion, skin contact, or inhalation--all possible routes of exposure in routine clinical use. Mice fed massive quantities of AC for prolonged periods of time exhibited no detectable alterations from normal mice.

Uremic patients receiving 20-50 g AC per day orally for 4-20 months developed no adverse effects. There appears to be no inherent toxicity associated with the oral administration of therapeutic doses of AC. Activated charcoal did not produce harmful effects upon prolonged skin contact. The inhalation of AC by experimental animals resulted in accumulation of the AC dust in the pulmonary system without any significant health effects or the development of malignancies.

Adverse reactions have been observed during hemoperfusion. These include thrombosis, a slight decrease in arterial pressure, a fall in

platelet count and plasma fibrinogen, and the development of particulate charcoal deposits in the lung and visceral tissues (Hagstam et al., 1966; Sparks et al., 1971; Yatzidis, 1971). To prevent some of these complications various modifications and adjuncts to the original hemoperfusion devices have been used. Heparin (2.5 mg/kg body weight) has been given during a 60-minute perfusion to prevent coagulation. Fall in arterial pressure is due to adsorption of sympathomimetic agents to the AC (Horres et al., 1976) and/or a reduction in blood volume (Yatzidis, 1971). The intravenous infusion of solutions containing 50 mg phenylnephrine hydrochloride/l has been used to correct the hypotension (Yatzidis, 1971).

Some work has been done using coated AC hemoperfusion columns in an attempt to prevent the fall in circulating platelets and plasma fibrinogen and to reduce tissue deposits of particulate charcoal (Amdahl, 1975; Andrade, 1972; Chang and Malave, 1970; Chang et al., 1971; Chang et al., 1974; Davis et al., 1974; Gazzard et al., 1974; Sparks et al., 1971; Wilson et al., 1973; Yatzidis, 1971). The various biocompatible AC coating substances that have been tested include alkali hydroxyethyl cellulose acetate, collodion coating which is then coated with adsorbed albumin, glutaraldehyde cross-linked bovine albumin with polyhydroxyethylmethacrylate (polyHEMA), and methylcellulose collodion and albumin.

Thorough rinsing of the modern AC hemoperfusion cartridges with heparinized physiological saline is said to give adequate protection against tissue depostis of microscopic charcoal deposits.

ACCEPTABILITY AND ALTERNATIVES TO ACTIVATED CHARCOAL

In spite of the recommendation that AC be used to prevent the bioavailability of ingested poisons and that hemoperfusion be employed to

enhance elimination of systemic toxicants, AC is seldom used in clinics and it is not available in household emergency kits. Some of the reasons for this neglect of AC in clinical practice are: the advantages of AC have not been clearly demonstrated in terms of reduced morbidity and cost of medical care; AC's unimpressive label as a chemical substance rather than a pharmaceutical product specifically prepared for use in humans; a general unawareness among clinicians of the proper use and dosage of AC; and AC's nonesthetic appeal (it is black and messy to administer) (Hayden and Comstock, 1975).

Other adsorbents have been investigated as substitutes. These include anion and cathion exchange resins (Rosenbaum, 1972; Rosenbaum et al., 1968), cholestyramine (Dordoni et al., 1973), kaolin and talcum (Hayden and Comstock, 1975), atapulgit (Atkinson et al., 1971), alaskan montmorillonite (Smith et al., 1967), evaporated milk (Chin et al., 1969), and the "universal antidote" (Holt and Holz, 1963; Picchionni et al., 1966). However, none of these has the general applicability of AC.

Now, some 15 years after the initial publication recommending use of "the black bottle" (Holt and Holz, 1963), AC appears to be the single most valuable antidotal agent for intoxication--but it remains unpopular in clinical practice.

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TABLE E1[a]

SOME SUBSTANCES EFFECTIVELY ADSORBED BY ACTIVATED CHARCOAL

ORGANIC COMPOUNDS		
Alcohol	Ipecac	Phenol
Antipyrene	Methylene blue	Penicillin
Atropine	Parathion	Sulphonamides
Barbiturates	Morphine	Phenolphathailein
Cocaine	Muscarine	Ouinine
Cantharides	Nicotine	Stramonium
Camphor	Opium	Strychrine
Aigitalis	Oxalates	Salicylates
INORGANIC COMPOUNDS		
As	Sn	P
$HgCl_2$	Ag	Sb
$KMnO_4$	I	

[a]Adapted from Holt and Holz, 1963.

TABLE E2[a]

ADSORPTIVE CAPACITY OF ACTIVATED CHARCOAL IN VITRO.
g COMPOUND/100 g ACTIVATED CHARCOAL

Atropine sulphate	70
Aspirin, pH 1.0	28
Barbital	70
Cyclobarbital	30-35
Chlorpromazine hydrochloride	36
D-Amphetamine sulphate, pH 1.0	18
Ethyl alcohol	30
Ethyl alcohol	51
Ferrous sulphate	17
Fluphenazine dihydrochloride	35
Glutethemide	50-60
Imipranine	125
Morphine hydrochloride	80
Malathion, pH 1	31
Mercuric chloride	180
Nicotine	70
Phenylpropanolaride, pH 1.0	10
Phenobarbital	30-35
Pentobarbital	32
Promethazine hydrochloride	33
Promazine hydrochloride	41
Prochlorperazine dihydro chloride	36
Propoxyphene hydrochloride	13
Propoxyphene hydrochloride	14
Potassium cyanide	35
Salicylic acid	55
Salicylamide, pH 1.0	37
Sodium salicylate, pH 1.0	49
Sodium salicylate, pH 1.6	20-25
Sodium pentobarbital	25

TABLE E2 (Continued)

Sodium hexabarbital	30-35
Sodium aprobarbital	30-35
Strychrine nitrate	14
Strychnine, pH 1	95
Sulfanilamide	100
Tripelennamine hydrochloride, pH 1.0	11
Thioridazine hydrochloride	30

[a]Adapted from Hayden and Comstock 1975.

TABLE E3[a]

ADSORPTIVE CAPACITY OF ACTIVATED CHARCOAL IN SIMULATED GASTRIC JUICE

EXOGENOUS PRODUCTS (DRUGS)

Very Efficiently Adsorbed	Efficiently Adsorbed
D-Amphetamine	Quinacrine
Primaquine	Meprobamate
Chlorpheniramine	Chlorpromazine
Colchiraine	Quinine
Diphenylhydantoin	Chloroquine
Aspirin	Quinidine
Iodine	Glutethimide
Phenol	2-4-Dichlorophenoxyacitic acid
Propoxyphene	Methyle salicylate

Poorly Adsorbed	Not Adsorbed
Ferrous sulphate	Mineral acids
Malathion	Alkali
DDT	Water insoluble compounds
N-Methylcarbamate	
Boric acid	

ENDOGENOUS PRODUCTS

Adsorbed	Not Adsorbed
Creatinine	Urea
Uric acid	Calcium
Guanidine	Phosphate
Ammonia	Albumin
	Total protein

[a]Adapted from Hayden and Comstock, 1975.

BINDING OF SELECTED TOXICANTS TO ACTIVATED CHARCOAL

by

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AN ABSTRACT OF A MASTER'S THESIS

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Activated charcoal (AC) is currently the single most valuable treatment for poisonings. It is used as a gastrointestinal sequestrant for orally ingested poisons and is recommended for hemoperfusion to detoxify blood of exogenous and endogenous poisons. We investigated the in vitro adsorptive affinity of AC as a powder and in activated charcoal hemoperfusion cartridges (ACC) for three human and animal toxicants: barbital, ethylene glycol (EG) and sodium fluoride (NaF). The in vivo usefulness of ACC hemoperfusion in dogs poisoned by barbital and EG was also studied.

Barbital, EG or NaF was added to freshly drawn heparinized canine blood, and AC (at 4 times the amount of toxicant) was added to the blood-drug mixture and maintained at 37°C. Whole blood or plasma levels of the respective toxicants were determined before and after adding AC at 15-minute intervals for 3 hr by the methods of Golbaum (1952) for barbital, Harger and Forney (1959) for EG, and Orion (1975) for NaF. Citrated ovine blood at 37°C containing barbital, EG or NaF was circulated through the ACC hemodetoxifier and levels of the free toxicants determined before and during circulation through the cartridge. Barbital or EG poisoning was induced in male and female dogs. Three barbital-poisoned dogs were hemoperfused for 3 hr with ACC, and two poisoned dogs (control) were hemoperfused for the same time without the cartridge in the circuit. Two EG-poisoned dogs were hemoperfused with 1 ACC in the circuit, two dogs with 2 ACC being utilized, and one dog (control) without an ACC.

The in vitro AC and ACC studies showed that barbital was well absorbed (45.9% on the powder and 100% on the cartridge), the EG was moderately absorbed (19.5% on the powder and 34.3% on the cartridge), and NaF poorly absorbed (4.2% on the powder and 0.8% on the cartridge). Two

barbital-poisoned and ACC-hemoperfused dogs showed rapid decreases in blood barbital levels and clinical recovery as compared to death in the controls. A barbital-poisoned dog hemoperfused with ACC for only 1½ hr survived longer than any of the control dogs. All EG-poisoned dogs died, but those hemoperfused with one ACC had blood EG levels decreased 66.7% of initial concentrations, while those hemoperfused with 2 AC had EG blood levels of only 54.2% the initial concentration after the 3 hr perfusion.

It was concluded that: (1) the in vitro absorptive affinity of AC and ACC are excellent for barbital, moderate for EG, but poor for NaF; (2) the in vivo ACC adsorption of barbital was good, but was relatively poor for EG; (3) the use of 2 instead of 1 ACC in the circuit produced a more pronounced decrease in EG blood levels, but no clinical benefit resulted; (4) ACC hemoperfusion therapy for barbital poisoning is safe and effective; and (5) this technique should be investigated further with other clinical intoxications.