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Modification of Phencyclidine Intoxification and Biodisposition by Charcoal and Other Treatments

JAMES E. LYDDANE, BRIAN F. THOMAS, DAVID R. COMPTON AND BILLY R. MARTIN[1]

Department of Pharmacology and Toxicology, Medical College of Virginia Virginia Commonwealth University, Richmond, VA 23298

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LYDDANE, J. E., B. F. THOMAS, D. R. COMPTON AND B. R. MARTIN. *Modification of phencyclidine intoxication and biodisposition by charcoal and other treatments*. PHARMACOL BIOCHEM BEHAV 30(2) 371–377, 1988.—Studies were conducted to determine whether single or combination treatments of charcoal, paraffin, cholestyramine, and/or ammonium chloride (NH_4Cl), would alter the rotarod-measured motor dysfunction induced by 10 to 90 mg/kg of phencyclidine (PCP). Additionally, the effect of NH_4Cl/charcoal treatment of the biodisposition of 50 mg/kg PCP was evaluated in order to assess whether amelioration of behavioral effects could be correlated to alterations in brain levels, plasma levels, and/or the renal clearance of PCP and metabolites. NH_4Cl/charcoal treatment proved more effective at reducing intoxication than either treatment singly, though effectiveness was reduced by larger doses of PCP. NH_4Cl/charcoal treatment reduced intoxification by 40, 16, and 21% at PCP doses of 10, 25, and 50 mg/kg. However, the reduction in motor dysfunction observed at 25 and 50 mg/kg PCP was greater than the sum of the individual treatments. In contrast, the effect of combined NH_4Cl and charcoal treatment on the biodisposition of 50 mg/kg PCP is not synergistic, but appears instead to be due simply to the additive effects of the individual treatments. Thus the amelioration of PCP intoxication cannot be fully explained by alterations in PCP biodisposition.

Phencyclidine Biodisposition Charcoal treatment Ammonium chloride treatment Paraffin treatment Cholestyramine treatment Rotarod performance

PHENCYCLIDINE (PCP) abuse occurs through a number of routes of administration, including oral ingestion, intravenous injection, and inhalation by snorting or smoking [13]. These various routes reportedly produce similar effects, differing primarily in the time of onset and duration of action. PCP's increased popularity since the early seventies is most likely due to the change in the preferred route of administration from oral ingestion to smoking [20]. However, PCP overdose often occurs following oral intake. PCP intoxication confronts medical professionals with a variety of symptoms, and the often labile recovery may require from several days to weeks.

No known antidote exists for treating PCP intoxication [12]. One approach to treatment is to increase renal clearance, which is normally very low [5], through an "ion-trapping" mechanism following acidification of the urine [1,12]. One method to produce renal (and gastric) acidification is through the oral administration of ammonium chloride (NH_4Cl). Clinicians have also successfully combined NH_4Cl treatments with gastric lavage to increase renal and gastric clearance of PCP among patients [1, 6, 9]. Additionally, treatment regimens which acidify the gastrointestinal tract produce an "ion-trapping" of PCP in the stomach, which reduces gastroenteric recirculation and increases removal of PCP by gastric lavage [6,9]. The oral adminstration of adsorbents also produces a type of "gut-trapping" [9,15]. Orally administered activated charcoal efficiently adsorbs various toxic substances and is often used in acute poisonings to prevent the gastrointestinal absorption of drugs [10]. Toxicological studies in laboratory animals support the rationalization of charcoal use for treatment of PCP intoxication by demonstrating a significant decrease in anesthesia and toxic symptoms, including death, when both substances were given concurrently [14]. Other potential adsorbents for treating PCP intoxication are cholestyramine, a nonabsorbable ion exchange resin, and liquid paraffin. Cholestyramine [4] and liquid paraffin [16] have been used successfully in treating poisoning from Kepone, which is (like PCP) a very lipophilic compound. The objectives of this study involve quantitating the effects of the aforementioned adsorbents, alone and in combination with urinary acidification via NH_4Cl treatment, on both PCP-induced motor dysfunction and PCP biodisposition. The oral route of PCP administration was chosen due to the fact that overdose is more likely to occur when this route is used.

[1]Requests for reprints should be addressed to B. R. Martin, Ph.D.

METHOD

Materials

Male Sprague Dawley rats, obtained from Dominion Laboratories (Dublin, VA), received food and water ad lib. They were housed individually in metabolic chambers (Wahmann Manufacturing Company, Timonium, MA) which allowed urine to be collected. ^{3}H-PCP (provided by the National Institute on Drug Abuse) with purity greater than 95% as determined by thin layer chromatography, was diluted with unlabeled PCP·HCl to an appropriate specific activity for use in the biodispositional studies. All doses and tissue concentrations are expressed in terms of the HCl salt. Questran (Mead-Johnson, Evansville, IN), which contains 44% anhydrous cholestyramine, was diluted with the appropriate quantity of distilled H_2O. Doses are expressed in terms of cholestyramine rather than Questran. Paraffin oil, a light mineral oil (Saybolt Viscosity 125/135) was purchased from Fisher Scientific (Fair Lawn, NJ) and administered without dilution. Norite A decolorizing carbon (activated charcoal) was obtained from Pfanstiehl Laboratories, Inc. (Waukegan, IL) and diluted with distilled H_2O to a concentration of 1 g/10 ml.

Rotarod Activity

A method similar to that described by Thomas *et al.* [19] was employed for the measurement of rat motor performance. Naive rats were trained to remain on a rotating (4 rpm) rod (6 cm in diameter) for 60 sec. They were subjected to ten trials no earlier than one day prior to the experiment. Those animals which failed to complete the task at the end of the tenth trial were discarded. A single trial immediately before the PCP administration supplied a baseline of motor ability. Animals were tested repetitively at designated times following the PCP administration in order to determine the time course of intoxication. A 60-sec cut off was utilized for each test. The amount of time the animals remained on the rotarod was recorded so that means±S.E. could be calculated for each time point, and compared to control values using ANOVA and Dunnett's *t*-test. In addition, the data were expressed as percent of baseline response (60 sec), plotted versus time, and the magnitude of effect for each treatment was determined by calculating area under the curve (AUC) using the Trapezoidal rule, and compared to control using ANOVA and Dunnett's *t*-test.

Quantitation of ^{3}H-PCP and Metabolites in Tissues

At various times after ^{3}H-PCP administration (50 mg/40 μCi/kg), rats were decapitated and the blood from the cervical wound collected in heparinized tubes which were centrifuged at 1000×g for 20 min. The plasma was removed and stored in 4-ml glass vials. In order to treat plasma in an identical fashion as other tissues, a 1-ml aliquot was removed and homogenized in 3 ml of 0.5 N HCl with a polytron (Brinkman Instruments, Westbury, NY). Total radioactivity was determined in the plasma by solubilizing a 300-μl aliquot as described below. Urine was collected from the time of PCP administration until decapitation and was treated in a manner similar to that described for plasma. Whole brains were removed and homogenized in 3 ml of 0.5 N HCl. A protocol similar to the procedure of Thomas *et al.* [19] was used to extract and quantitate tissue concentrations of ^{3}H-PCP. One-ml aliquots of the tissue homogenates were buffered with 1 ml KH_2PO_2 (20% w/v), and adjusted to pH 9.5 with 2 N NH_4OH. Hexanes (10 ml) were added and the samples were shaken for 10 min. Samples were centrifuged for 10 min at 3000×g, and 8 ml of the hexane layer was removed and added to 10 ml of TPP scintillation fluid [126 ml of Liquifluor PPO-POPOP (NEN Research Products, Boston, MA) in 3 l of toluene]. The extracted radioactivity (^{3}H-PCP) was quantitated by conventional liquid scintillation spectrometry, with external standardization used to correct for quenching. It has been demonstrated previously that this extraction technique is both quantitative and qualitative [19]. To measure total drug (PCP + metabolite) radioactivity, 300-μl aliquots of brain homogenate, plasma, and urine were solubilized in 2 ml TS-2 (RPI, Mount Prospect, IL) for 24 hr. After neutralizing the samples with 75 μl of glacial acetic acid and adding 10 ml of TPP, the total radioactivity of the (unextracted) samples was measured. The metabolites present were quantitated by substracting the radioactivity present as (extracted) ^{3}H-PCP from the total radioactivity. The primary metabolites present in the brain, plasma, and urine under these conditions are the monohydroxyalted metabolites [PPC—4 phenyl-4-piperidinocyclohexanol, and PCHP—1-(1-phenylcyclohexyl)-4-hydroxypiperidine], plus dihydroxylated PCP metabolites, and more polar metabolites {PCAPA—5-[N-(1-phencyclohexyl) amino] pentanoic acid}, as well as conjugated metabolites in the plasma (conjugated PPC and PCPH). Data were analyzed using Dunnett's *t*-test.

Treatment Protocol

The wide variety of treatment groups (N=6–12 rats per group) were evaluated for alteration of PCP-induced motor dysfunction (see Table 1). A limited number of treatment groups (N=6 per group) were evaluated for alteration of PCP biodisposition (see Table 2). In the charcoal regimen, the animals were gavaged once with PCP (10, 25, or 50 mg/kg in a volume of 2 ml/kg) followed by hourly oral treatments beginning 45 min later. The individual treatments consisted of either charcoal (1 g/kg), NH_4Cl (2.5 mEq/kg) or an equivalent amount of water. The NH_4Cl/charcoal treatment regimens consisted of one of the following gavages at hourly intervals for a total of 6 hr: 6 water (controls); 3 NH_4Cl alternating with 3 water; 3 water alternating with 3 charcoal; 3 NH_4Cl alternating with 3 charcoal. Rotarod testing continued throughout until complete recovery occurred (up to 10.5 hr after PCP administration).

Other adsorbent treatments were conducted using a protocol similar to that described for charcoal. Initially three treatments of liquid paraffin (1 g/kg) were administered orally at hourly intervals beginning 1 hr after PCP (50 mg/kg, PO). Subsequently, the number of liquid paraffin treatments were increased to five. Additionally, a combination NH_4Cl/paraffin treatment was tested using a protocol identical to that used with NH_4Cl/charcoal treatment, except the dose of paraffin was increased to 2 g/kg. Lastly, cholestyramine treatment (1 g/kg×3) was compared to charcoal (1 g/kg×3) after a 90 mg/kg dose of PCP. The treatments were given every 2 hr beginning 45 min after PCP administration, with subsequent testing of the animals in the rotarod procedure.

RESULTS

Rotarod

The effectiveness of cholestyramine and charcoal in attenuating PCP-induced motor dysfunction was evaluated. Rats were given PCP (90 mg/kg, PO) followed by oral ga-

TABLE 1

AUC VALUES FOR VARIOUS TREATMENT GROUPS

PCP Dose	Hourly Treatments	Mean ± S.E.	%*
10 mg/kg	Control [Water (6)]	149 ± 24	100
	NH_4Cl (3)/Water (3)	116 ± 23	78
	Water (3)/Charcoal (3)	105 ± 26	70
	NH_4Cl (3)/Charcoal (3)	90 ± 21	60
25 mg/kg	Control [Water (6)]	367 ± 17	100
	NH_4Cl (3)/Water (3)	400 ± 18	109
	Water (3)/Charcoal (3)	354 ± 18	96
	NH_4Cl (3)/Charcoal (3)	308 ± 13	84
50 mg/kg	Control [Water (6)]	620 ± 35	100
	NH_4Cl (3)/Water (3)	560 ± 49	90
	Water (3)/Charcoal (3)	621 ± 49	100
	NH_4Cl (3)/Charcoal (3)	490 ± 19	79
	Control [Water (3)]	560 ± 45	100
	Paraffin [1 g/kg (3)]	601 ± 40	107
	Control [Water (5)]	708 ± 48	100
	Paraffin [1 g/kg (5)]	613 ± 60	87
	Control [Water (6)]	551 ± 37	100
	NH_4Cl (3)/Water (3)	482 ± 34	87
	Water (3)/Paraffin [2 g/kg (3)]	572 ± 29	104
	NH_4Cl (3)/Paraffin [2 g/kg (3)]	458 ± 36	83
90 mg/kg	Control [Water (3)]†	1810 ± 73	100
	Charcoal [1 g/kg (3)]†	1406 ± 111	78
	Cholestyramine [1 g/kg (3)]†	1774 ± 141	98

Values are means (N=6–12 per group) calculated from initial treatment to time of recovery, and analyzed by ANOVA with Dunnett's *t*-test. Numbers in parentheses indicate the number of treatments.

*Values less than 100% (i.e., water control) represent decreases in total time of intoxication.

†Treatments were at 2 (not 1) hour intervals.

vages of either charcoal (1 g/kg×3), cholestyramine (1 g/kg×3) or an equivalent quantity of water every 2 hr beginning 45 min after PCP administration. The control (water-treated) animals recovered complete motor function at 27 hr. The charcoal-treated animals recovered by 24 hr. The AUC was calculated from 45 min after PCP treatment to the time of recovery (Table 1). Charcoal treatment did reduce PCP-induced motor dysfunction to 22%, although the effect was not statistically significant. Cholestyramine treatment had a very small (2%) effect on the magnitude of PCP's effects.

The ammonium chloride and charcoal treatments, either separately or in combination, produced no significant effect on PCP intoxication at individual time points after 50 mg/kg PCP (Fig. 1A), or at either 10 or 25 mg/kg PCP (data not shown). However, calculation of AUC (% effect from 45 min to the time of recovery) revealed that each treatment produced slight decreases in motor impairment compared to control values (Table 1). The combined treatment produced the greatest degree of recovery at all doses of PCP. However, this attenuation of motor impairment was not statistically significant.

Experiments were also conducted to determine the effect of liquid paraffin treatment on decrements in rotarod performance produced by 50 mg/kg PCP (Table 1). Three gavages of 1 g/kg liquid paraffin at hourly intervals beginning 45 min after PCP administration produced a slight (7%) increased motor impairment. Increasing the number of gavages to five resulted in a minor (13%) reduction in motor dysfunction. When evaluating the effectiveness of combination NH_4Cl/paraffin treatment, the paraffin dose was increased to 2 g/kg and administration was identical to the NH_4Cl/charcoal regimen. The treatments of paraffin and NH_4Cl, either alone or in combination, failed to produce statistically significant differences at individual time points after 50 mg/kg PCP (Fig. 1B), or at either 10 or 25 mg/kg PCP (data not shown). The AUC's for the rats receiving 50 mg/kg PCP were not significantly different from each other (Table 1). Since water/paraffin treatment did not ameliorate motor dysfunction and combined treatment was no more effective than NH_4Cl/water, the effect of NH_4Cl/paraffin treatment appears to be primarily due to the presence of the NH_4Cl.

Biodispositional Studies

Since the rotarod studies demonstrated some effect of the combined NH_4Cl/charcoal treatment on the time course of PCP-induced changes in rotarod performance, an investigation was undertaken to quantitate the effects of this treat-

TABLE 2

EFFECTS OF NH_4Cl AND CHARCOAL TREATMENT ON THE BIODISPOSITION OF ^{3}H-PCP (50 mg/kg, PO)

Hr	Treatment	Brain (μg/g)	Plasma (μg/ml)	Urine (total μg)
			^{3}H-PCP·HCl	
6	Water	1.66 ± 0.12	0.27 ± 0.03	451 ± 153
	NH_4Cl	1.32 ± 0.16	0.28 ± 0.04	1234 ± 342†
	Charcoal	1.58 ± 0.17	0.25 ± 0.05	632 ± 213
	NH_4Cl/Charcoal	1.17 ± 0.24	0.23 ± 0.03	951 ± 324*
10	Water	0.66 ± 0.04	0.12 ± 0.01	259 ± 59
	NH_4Cl	0.58 ± 0.05	0.12 ± 0.01	749 ± 169†
	Charcoal	0.34 ± 0.05†	0.06 ± 0.01†	139 ± 45*
	NH_4Cl/Charcoal	0.40 ± 0.04†	0.07 ± 0.01†	587 ± 116†
24	Water	0.26 ± 0.03	0.03 ± 0.02	515 ± 51
	NH_4Cl	0.19 ± 0.02*	ND	1087 ± 155†
	Charcoal	0.16 ± 0.02†	ND	444 ± 72
	NH_4Cl/Charcoal	0.16 ± 0.02†	0.01 ± 0.02	734 ± 97*
			Metabolites[a]	
6	Water	3.48 ± 0.51	4.84 ± 0.22	3660 ± 661
	NH_4Cl	3.09 ± 0.35	4.24 ± 0.24	4220 ± 559
	Charcoal	2.90 ± 0.42	4.39 ± 0.36	3770 ± 653
	NH_4Cl/Charcoal	2.72 ± 0.55	4.27 ± 0.22	3600 ± 798
10	Water	2.81 ± 0.28	4.40 ± 0.26	2330 ± 249
	NH_4Cl	2.43 ± 0.16	4.18 ± 0.11	3080 ± 212†
	Charcoal	1.79 ± 0.13†	2.94 ± 0.20†	1510 ± 176*
	NH_4Cl/Charcoal	1.89 ± 0.25†	3.46 ± 0.18†	2390 ± 268
24	Water	2.13 ± 0.13	3.87 ± 0.18	3990 ± 273
	NH_4Cl	2.57 ± 0.11	3.86 ± 0.13	4360 ± 181
	Charcoal	1.93 ± 0.23	3.10 ± 0.12†	3270 ± 200
	NH_4Cl/Charcoal	1.68 ± 0.09	3.01 ± 0.19†	3270 ± 278

Significantly different from the water-treated control by Dunnett's *t*-test at *$p<0.05$ or †$p<0.01$.

Results of each group (N=6) are presented as means ± S.E.

[a]Metabolites measured are primarily the monohydroxylated metabolites (PPC, PCHP), dihydroxylated metabolites, and more polar metabolites (e.g., PCAPA), as well as a variety of conjugated metabolites in the plasma (conjugated PCHHP and PPCH).

ment on the biodisposition of ^{3}H-PCP (Table 2). After treatment with a combination of NH_4Cl/charcoal, the concentrations of both ^{3}H-PCP and its metabolites in the brain and plasma at 10 hr were significantly less than those in the corresponding tissues in the control animals. Urinary excretions partially corroborate the observed decreases by showing a two-fold increase in the output of ^{3}H-PCP (but not metabolites) at 6 and 10 hr. A smaller, but significant, increase in ^{3}H-PCP excretion was also present at 24 hr, a period at which brain ^{3}H-PCP concentrations were also reduced. However, a greater enhancement of urinary ^{3}H-PCP excretion occurred with the NH_4Cl treatment alone, with three-fold increases at 6 and 10 hr, and a two-fold increase at 24 hr. Interestingly, the charcoal treatment alone, like the combination treatment, decreased brain and plasma levels of both ^{3}H-PCP and its metabolites at 10 hr, as well as brain PCP levels at 24 hr. However, in contrast to the combined treatment, charcoal alone decreased the urinary output of both PCP and metabolites at the 10 (but not 6 or 24) hr period. These data suggest that combined NH_4Cl/charcoal treatment primarily decreases brain and plasma levels of ^{3}H-PCP and metabolites via the actions of charcoal, while increases in the renal excretion of ^{3}H-PCP are primarily due to the action of NH_4Cl.

DISCUSSION

Cholestyramine treatment (1 g/kg) did not significantly alter the behavioral effects of 90 mg/kg PCP which seems to suggest that there is limited adsorption of PCP by cholestyramine. In contrast to these negative results, there are reports describing the successful adsorption in rats of another highly lipophilic drug, Kepone [4]. In fact, Boylan *et al.* [4] suggest that cholestyramine treatment might offer a means of detoxifying patients exposed to a variety of lipophilic substances, and not just for treating those conditions ameliorated by the binding of intestinal bile salts. However, despite the fact that PCP is a very lipophilic drug that rapidly distrib-

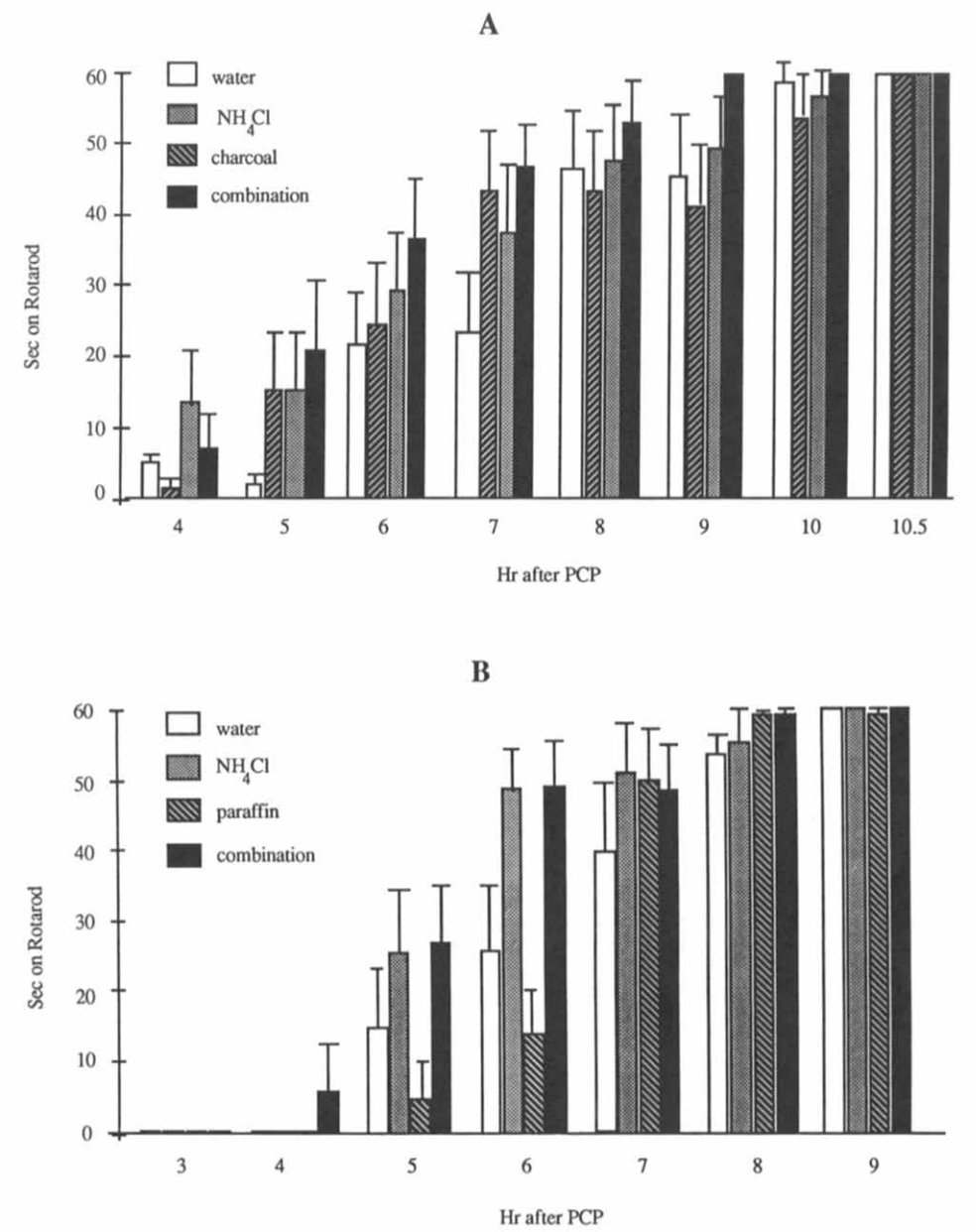

FIG. 1. The effects of various treatments with NH_4Cl and either charcoal (A) or paraffin (B) on the motor impairment induced by PCP (50 mg/kg, PO). The hourly treatments, as denoted in the figure, were initiated after PCP administration and continued for a total of 6 treatments (see the Method section). The time the animals remained on the rotarod are presented as means±S.E. for each group (N=6–12). The data were analyzed by ANOVA and Dunnett's *t*-test.

utes itself into body lipids [18], there may be good reasons to expect limited adsorption by cholestyramine. Cholestyramine (Questran) is supplied as the chloride salt of a basic anion exchange resin, and the chemical structure is that of a polymer with a quaternary nitrogen group. The permanent positive charge of the quaternary nitrogen is the functional site of the anion exchange, and therefore effectively adsorbs bile acids. This will subsequently lead to reduced gastrointestinal absorption of fat soluble compounds, like vitamins A, D, and K. However, PCP is a basic compound, and is therefore positively charged at gastric pH levels, and would not undergo ion exchange with the anion exchange resin. Therefore, these data indicate that the adsorption of lipophilic drugs by cholestyramine is secondary in nature to the essential mechanism of action (anion exchange) of the resin, and thus this resin may not be as useful a detoxifying treatment as has been suggested.

Rats have also been treated for Kepone toxicity with paraffin [16]. Paraffin reduced tissue levels of Kepone, but not as effectively as it reduced levels of another lipophilic drug, hexachlorobenzene [16]. Initial data suggested that paraffin might be useful in reducing the behavioral effects of

PCP, presumably by trapping PCP. Hourly doses of paraffin (5×1 g/kg) following 50 mg/kg PCP resulted in a decrease in PCP-induced motor impairment by 13% (AUC). When the treatment was decreased to 3 hourly treatments, the paraffin group's motor ability was increased by 7% of the water-treated controls, indicating no beneficial effect of the treatment. Therefore, in subsequent experiments investigating the combined effects of NH_4Cl/paraffin, the paraffin dose was increased to 2 mg/kg. The combined treatment of NH_4Cl/paraffin produced a 17% (AUC) decrease in PCP-induced motor dysfunction. However, the NH_4Cl/water treatment alone produced a similar (13%) effect, while water/paraffin alone did not alter motor dysfunction.

Oral administration of activated charcoal reduces the behavioral effects of a variety of drugs such as barbiturates [3,10], anti-inflammatory drugs [10,11], cardiac glycosides [2,10] and others [10]. However, charcoal treatment, while being generally useful for a given class of drugs [10], may not always increase the clearance of a specific drug of that group [7]. Additionally, charcoal and /or NH_4Cl treatments appear to be of some use in reducing PCP intoxication both clinically [1, 6, 9, 15] and in laboratory animals [14]. However, attempts to alter PCP intoxication in other laboratory animals (rhesus monkey) have not been successful, even though renal clearance of PCP was increased by NH_4Cl treatment [17]. The monkey data also indicated great inter-animal variability in the AUC analysis of serum levels, total body clearance, and renal excretion of PCP [17]. Similar variability has been observed in renal excretion [12] and plasma levels [6] of PCP in humans. This variability in PCP pharmacokinetics, like the variability in the period of PCP-induced intoxication and recovery [15], may be partially due to the high degree of gastroenteric recirculation of PCP [6,9] in combination with sequestration of the drug into body lipids with subsequent release back into the blood stream [18]. Charcoal treatment would be expected to interrupt these processes and reduce intoxication. Preliminary data in this report indicated that charcoal treatment did decrease the detrimental effects of PCP on motor ability, and was therefore investigated more thoroughly in combination with NH_4Cl treatment. However, the beneficial effects of these treatments were only observed after AUC analysis, and not by statistical analysis at individual time points. This may be attributed to the fact that there is a large degree of inter-animal variability in PCP metabolism, excretion, and motor dysfunction, similar to that observed by others [6, 12, 15, 17].

It has been shown that the oral administration of NH_4Cl reduces rat urine pH to a minimum of 5.5 [19], and should therefore increase renal excretion of PCP. Additionally, the decrease in gastric pH should also increase gastric levels of PCP by the "gut-trapping" mechanism, which might increase the amount of PCP that could be adsorbed by charcoal. The combination of these treatments would then be expected to ameliorate PCP's effects to a greater extent than either treatment alone. The results presented herein do indicate that the NH_4Cl and charcoal treatments alone were not nearly as effective in altering PCP-induced motor dysfunction as these treatments in combination. The combined treatments decreased the motor debilitating effect of PCP, as measured by AUC, by 16 to 40% of control values. The degree of protection conferred by NH_4Cl/charcoal treatment decreased, as would be expected [10], as the dose of PCP increased from 10 to 50 mg/kg. Although the degree of protection afforded by NH_4Cl/charcoal treatment is only moderate, there was no consistent effect of NH_4Cl or charcoal treatments alone. Therefore, on the basis of the reduction of AUC values of PCP-induced motor impairment over a period of 1 to 11 hr, it appears that NH_4Cl/charcoal is indeed more effective than either treatment alone. This increased efficacy of detoxification might be attributed to decreased quantities of PCP at the active site (presumably the brain) due to increased renal clearance combined with increased charcoal adsorption of PCP.

Treatment of rats with NH_4Cl produced increases in renally excreted PCP by three-fold at 6 and 10 hr, and by two-fold at 24 hr post-PCP administration. As expected, increases in metabolites were either not observed, or were small. The lack of an increase in the renal excretion of PCP metabolites following NH_4Cl treatment has been observed by others, even though PCP clearance was increased eight-fold [12]. Additionally, the lack of an alteration in PCP-induced behavior in laboratory animals by NH_4Cl treatment has also been observed, even though renal clearance was increased [17,19]. The lack of a consistent reduction of PCP-induced motor dysfunction by NH_4Cl found in this study, as well as in another report [19], is further supported by the fact that neither PCP nor metabolite levels were altered in the plasma or brain at any time, with the exception of a decrease in brain PCP at 24 hr. It is possible that this decrease is a result of the prolonged increase in renal PCP clearance produced by NH_4Cl, but the alteration is apparently not sufficient to protect from PCP toxicity. Others have also shown that acidification of the urine may lead to increased renal clearance without changes in plasma levels of PCP [12]. It is also likely that the degree of increase in renal PCP clearance in rats is not as great as the 4-, 8-, or 200-fold increases observed by others [6, 9, 12], because the reduction of urine pH to 5–6 (the maximum that occurs in rats in these experiments) is only half as effective as reduction of pH to less than 5 [6,9].

Charcoal treatment alone produced no protection from 50 mg/kg PCP-induced motor dysfunction. However, concentrations of PCP and metabolites were reduced in plasma and brain at 10 hr. There was also a reduction of brain PCP concentrations at 24 hr. Interestingly, charcoal reduced renal excretion of PCP and metabolites at 10 hr which may indicate some minimal shifting of PCP from renal compartments to gastric ones. A shift of this nature would tend to reduce NH_4Cl-induced increases in renal excretion of PCP (discussed below). Since the dose of charcoal used was large (3×1 g/kg) compared to the dose of PCP (10–50 mg/kg), it seems unlikely that further protection would be afforded by increasing the treatment regiment. However, the results of charcoal treatment following lower doses of PCP support the reports of others showing decreased PCP toxicity in laboratory animals due to charcoal treatment [14].

The NH_4Cl/charcoal treatment was the most effective regimen for reducing PCP-induced motor dysfunction. However, the magnitude of increase in the renal clearance of PCP following NH_4Cl/charcoal treatment was actually smaller than that observed with NH_4Cl alone. It might be assumed that the net decrease in brain or plasma levels of PCP with combined treatment would be greater than with either treatment individually because of "gut-trapping" and charcoal adsorption in addition to significant ion-trapping of PCP in the urine. However, the magnitudes of the decreases observed in plasma and brain levels of either PCP or metabolites following NH_4Cl/charcoal treatment were not different from that observed with charcoal alone. It is possible that gastric acidification by NH_4Cl does not increase charcoal

adsorption of PCP, and therefore does not further alter plasma PCP levels. It is true that gastric acidification does increase the gastric clearance of PCP when the stomach contents are removed by lavaging [1,6], however, the clearance is at most only doubled compared to the control, and small compared to total body clearance [1, 6, 9], despite the fact that PCP levels in the gastric juices of patients are 20–50-fold higher than plasma levels [6]. Similarly high levels of PCP have been found in the stomachs (tissue plus contents) of rodents following oral administration of PCP [8]. Thus, the effect of combined NH_4Cl/charcoal treatment on PCP biodisposition appears to be a summation of the effects of each of the individual treatments. Therefore, the reasons for the increased efficacy of combination treatment on the reduction of PCP intoxication is unclear. Perhaps there is a redistribution of PCP within various intracellular and/or extracellular body compartments following NH_4Cl administration (similar to the explanation given by Done *et al.* [6] to explain fluctuations in plasma PCP levels), which is responsible for the increased efficacy of NH_4Cl/charcoal treatment.

It is noteworthy that NH_4Cl/charcoal treatment was only moderately effective in ameliorating PCP intoxication. The reasons for the minimal efficacy of the NH_4Cl/charcoal treatment in reducing either the behavioral effects of PCP or the alteration of PCP biodisposition in a pattern commensurate with those beneficial effects, are unclear. However, the major premise of such treatments is that there is a large increase in the total body clearance of PCP. The renal clearance of PCP in both man [5] and some laboratory animals [3] is only 9–10% of the total body clearance, and acidification of the urine to pH 5 or less only increases renal clearance to a calculated 28% [9]. If a similar situation is assumed to be true for the rat, then the pH 5.5 of rat urine produced in these experiments by NH_4Cl would only be half as effective as increasing renal clearance relative to total body clearance [9]. Perhaps this is why no greater effect on PCP-induced intoxication was observed following the administration of NH_4Cl. However, it may be possible to increase the effectiveness of urine acidification in the rat by simultaneous administration of the diuretic furosemide, as has been done clinically [1, 6, 15]. Enhancing urinary flow by four-fold, in conjunction with acidification of urine to pH 4.5, reportedly increases renal clearance of PCP to over half of the total body clearance value [9]. Therefore, combination treatments still hold promise for decreasing PCP intoxication, and should be evaluated further in hopes of finding a more efficacious therapy for reducing PCP intoxication in humans, and in determining the mechanisms by which reduction of intoxication occurs.

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