Effects of urine acidification on plasma and urine phencyclidine levels in overdosage

A gas chromatography–mass fragmentography–electron impact (GC-MS-EI) assay of phencyclidine (PCP) was adapted for human plasma and urine. This assay is specific for PCP and very sensitive (approximately 1 ng/ml). Patients with the putative diagnosis of PCP overdosage were studied to correlate plasma and urinary levels with clinical state. Urinary PCP levels were enhanced in an acid urine, which suggests that acidification of the urine is an adjunct in the therapy of PCP overdosage.

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Phencyclidine (PCP, hog, angel dust, crystal THC, peace pill) is currently an important drug of abuse.[6, 7, 10–12] Chen and associates[3] first described its pharmacologic properties and suggested its use as a general anesthetic in man. It was subsequently dropped from further clinical trials when a large percentage of patients showed prolonged emergence delirium. The drug produces an unusual psychosis in normal people which is a useful "model" of schizophrenia.[4, 5, 9] Currently, its only therapeutic use is as an anesthetic in veterinary medicine. Its illicit use in the drug subculture is widespread, partly due to the ease of its synthesis and its reinforcing properties. The determination and identification of PCP in biologic fluids and tissues is of obvious interest. With the availability of gas chromatography–mass spectrometry (GC-MS) it is now possible to obtain positive and quantitative identification of this drug. We have reported a GC-MS electron impact (EI) assay for measuring PCP plasma pharmacokinetics in the dog and monkey.[13]

The purpose of this paper is to report on the PCP levels in human plasma and urine during states of intoxication. We also present suggestive data on acidification of the urine as a possible means of enhancing PCP urinary excretion.

Methods

Hospitalized patients reported to be intoxicated with PCP were the subjects of this study. They were referred to us for positive identification of PCP as well as for suggestions on therapy. Whole blood was collected in heparinized tubes and spun at 1,000 g for 15 min, and the plasma was removed for PCP extraction. Urine was collected in standard urine containers. The color and pH were noted at the time of collection, if possible. Samples were frozen at −20° C until they could be extracted. Usually 1 to 2 ml of plasma was drawn for analysis. The volume of urine varied from 1 to 10 ml, depending upon availability and degree of intoxication. The most practical way was to assay a few random samples before extracting all of them,

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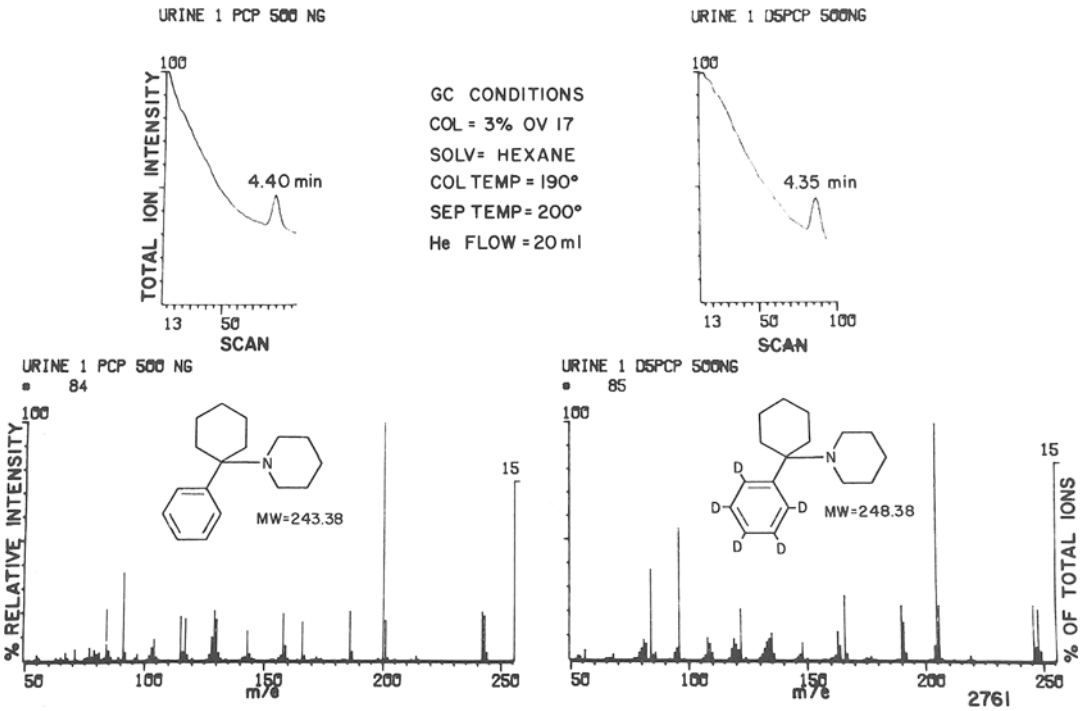

Fig. 1. Total ion chromatograms and mass spectra of phencyclidine and d_5-phencyclidine in human urine. Note similar retention times of PCP and d_5-PCP. Note that m/e 91 and 200 for PCP and m/e 96 and 205 for d_5-PCP are the major ions. A small molecular ion M^+ is seen for each. Specific retention times vary depending upon density of column packing, flow, etc.

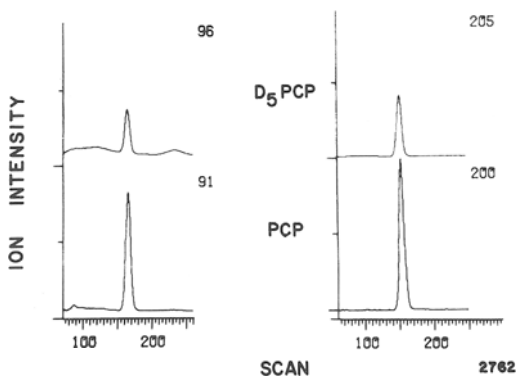

Fig. 2. Mass fragmentogram of an extracted urine in a case of PCP overdosage. The ions m/e 91, 200 and 96, 205 were monitored for PCP and d_5-PCP, respectively. Note that there is much more PCP than the added d_5-PCP. This was calculated to be 0.94 μg/ml of free PCP in the urine.

since these gave an idea of the amount of internal standard to add or amount of sample to take for analysis. The method of extraction and determination of PCP was adapted from Lin and co-workers.[8] This involves adding about 1 μg/ml of pentadeuterated PCP (d_5-PCP) to the sample as the internal standard.

The Finnigan 3200 system was used to monitor individual ion fragments. A 5 ft × 2 mm glass column of 3% OV-17 of Gas Chrom Q was used. The oven temperature was 190° C, injection port 200° C, and the glass jet separator at 210° C to prevent excessive thermal decomposition of PCP. In view of the fact that 91, 96, 200, and 205 m/e are the major fragments of PCP and d_5-PCP, respectively, these ions were monitored and peak area ratios taken for quantitation. This assay is described in detail by Wilson and Domino.[13]

Results

Validation of the assay for human plasma and urine. Venous blood and urine from normal human volunteers were used in the initial studies. These subjects were free from drugs for at least 1 wk. Varying amounts of PCP and 1 μg/ml of d_5-PCP were added to the plasma and urine samples and extracted. Approximately

1-μl amounts of extract, the total volume of which was 20 to 25 μl, was then injected into the GC-MS and a total ion chromatogram (TIC) obtained. In the upper portion of Fig. 1 is a typical TIC of normal human urine to which PCP and d_5-PCP were added in separate samples. Note the single GC peak containing PCP or the d_5-PCP. In the lower portion of Fig. 1 are the mass spectra of each. A typical mass fragmentogram is shown in Fig. 2. The data from one patient monitored over 4 days are given in Fig. 3, which shows the influence of urinary pH on the amount of PCP excreted. As urinary pH is decreased, PCP urine concentrations rise. The correlation coefficient was -0.63 with $p < 0.004$. During this period of time the patient continued to be comatose. Plasma PCP levels did not change markedly, as is shown in Table I.

When 0.01 N HCl acid was given along with an intravenous infusion of fluids, as pH decreased the urinary excretion of PCP increased. Urinary pH fell and rose rapidly as a function of the amount of 0.01 N HCl infused.

Upon complete recovery approximately 1 wk later, the patient claimed that he had taken 100 pills which we found to contain about 5 to 6 mg each of PCP. The patient was in a small hospital for 6 days before we started to monitor urine and plasma. During the 3.5 days the patient was monitored he excreted 11.04 mg of PCP as such. Inasmuch as this patient claimed to have ingested 500 mg total of PCP, the amount excreted unchanged is obviously very small. A portion was probably excreted during the preceding 6 days of hospitalization. However, the patient was still comatose. PCP could be sequestered in body tissues or could be primarily excreted as metabolites.[14]

Table II summarizes the amount of PCP found in human plasma and urine from samples taken simultaneously in a number of studies. Urine PCP concentrations range from 13- to 19-fold that of plasma.

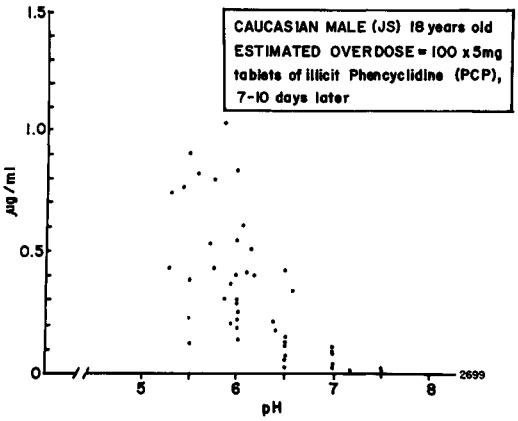

Fig. 3. Relationship between urinary pH and phencyclidine concentration in a patient with phencyclidine overdosage. Note that the lower the urinary pH the greater the PCP urinary concentration. During this period PCP plasma levels ranged from 40 to 91 ng/ml. The patient remained unconscious and recovered after approximately one week.

Table I. *Plasma PCP levels in one patient*

Time	*PCP (ng/ml)*
Day 1, 10 P.M.	58
Day 2, 10 A.M.	91
Day 3, 9 A.M.	40
Day 4, 10 A.M.	75

Table II. *Comparison of human plasma and urine levels from various PCP overdose cases*

Plasma levels (ng/ml)	*Urine levels (ng/ml)*	*pH*	*Reference*
49	910	—	Gupta et al.[7]
51	870	—	Gupta et al.[7]
63	863	—	Present
75	267	6.5	Present
90	850	6.4	MacLeod et al.[10]
91	090	7.4	Present
112	1,680	4.8	Present
116	1,430	5.5	Present
125	1,100	—	Present
190	2,750	—	MacLeod et al.[10]
3755	5,700	—	MacLeod et al.[10]

Discussion

Organic bases are generally acknowledged to be excreted in greater amounts in an acid urine. The pKa of PCP as yet has not been formally determined under standardized conditions that approximate those in the human organism. The pKa appears to be approximately 8 to 9. Amphetamines are perhaps the best known drugs, the excretion of which has clearly been shown to be related to urinary pH.[2] Recently, Aronow

and Done[1] have reported several PCP overdose cases treated with urinary acidification with similar results. We were privileged in assaying, under double-blind conditions, the urine and blood samples of their patients. In addition, some of the same samples were assayed by Dr. D. E. Lin of Battelle, Columbus, Ohio. Our data were very similar and will be the subject of another report.

Further studies on the treatment of PCP overdosage are clearly indicated. The relationship between pH of the urine and rate of excretion of the drug in the urine when plasma concentrations are known are the key issue rather than urinary pH and urinary concentration. Our limited plasma data indicate that the PCP levels did not change drastically over the interval the urine PCP levels were measured. It remains for research and clinical experience to decide on the practicality of such a simple procedure as urinary acidification in the treatment of PCP overdosage. Our patient showed considerable improvement after almost 10 days of coma. The role of acidification and forced diuresis in his recovery are not clear. Other suitable acidifying agents such as NH_4Cl should also be considered.

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