History and Pharmacology of PCP and PCP-Related Analogs†

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Relatively few humans have an opportunity to be involved in the discovery of new and potentially useful therapeutic agents. Those medicinal chemists, pharmacologists and physicians, among others, who are able to contribute to the development of a chemical which makes a significant impact on the suffering of humans, can indeed enjoy personal satisfaction for their efforts. However, when that chemical is wrongfully used and leads to further human misery one is indeed sad and depressed! Yet each new discovery can lead to much good and great harm to society. Consider the number of tragic fires, automobile accidents, plane crashes, gunshot wounds, bombing disasters and atomic catastrophes. The same is true of drugs. The abuse of many chemicals such as alcohol, LSD, marijuana and now phencyclidine (PCP) are good examples of human failure to rationally balance the good against the harm that each new discovery provides. I believe the final chapter of PCP has yet to be written.

HISTORY

It seems appropriate here to document the history of PCP and its derivatives. I would like to provide the perspective as a scientist and physician who has been involved in research to develop compounds for human illness. The present manuscript gives more details of what was previously reported in my chapter (Domino 1978) in the NIDA PCP monograph (Petersen & Stillman 1978) and a recent PCP book (Domino 1980).

PCP and its derivatives are the result of the initial discovery of a new and unexpected chemical reaction, then unexpected pharmacological activity and potential therapeutic merit, then disappointment and a subsequent systematic search for better chemical derivatives, again for potential therapeutic benefit. In recent years some self-styled chemists have made PCP and related derivatives under illicit conditions for either personal profit or to induce temporary madness in their fellow humans eager to expand or distort their minds. Humans, in their never ending quest to explore and discover, may yet find "a pot of therapeutic gold" at the end of a spectacular and at times rather dismal PCP rainbow. The common street names for PCP are listed in Figure 1.

FIGURE 1

STREET NAMES FOR PHENCYCLIDINE

PCP, Synthetic THC, Angel Dust, Dust, Hog, Crystal, Animal Tranquilizer, Horse Tranquilizer, Peace Pill, PeaCe Pill, Crystal Joint, CJ, KJ, Sheet, Rocket Fuel, Peace, Peace Weed, Supergrass, Super Kools, Superweed, Elephant Tranquilizer, Horse Tranks, Seams, Surfer, Snorts, Scuffle, Cadillac, Mist, Goon, Amoeba, Cyclones, DOA (dead on arrival), Killer Weed, Synthetic Marijuana, Lovely, Lovely High

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The story of PCP starts in 1956, just 24 years ago, when a medicinal chemist, Dr. Victor Maddox of the Product Development Department of Parke Davis and Company in Detroit, Michigan, began to investigate chemical reactions to Grignard reagents with nitriles. What that means is that there are special ways of making new organic chemicals of which the Grignard reagent is a classic one. Dr. Maddox was interested in elaborating some rather new, stable immino or ketone compounds with novel chemical structures which he hoped would have therapeutic merit. What actually occurred in the reaction using the chemicals, called α-aminonitriles, was a very unusual elimination of the nitrile function and substitution by rather large (what we called aryl or alkyl moieties) of the Grignard reagent. The second compound in this series made by Dr. Maddox, using this novel and unique reaction, was PCP itself. Having prepared adequate quantities of the first as well as the second of these compounds, Dr. Maddox submitted them to a pharmacologist by the name of Dr. Graham Chen at Parke Davis for general pharmacological testing. This testing was known as the GP (for general pharmacological) series and PCP was assigned number GP 121 as its code name. Shortly thereafter, about a week after Dr. Maddox submitted the material, Dr. Chen called Dr. Maddox and excitedly told him that GP 121 was the most unique compound that he, Dr. Chen, had ever examined. He called it a "cataleptoid anesthetic" and because of it, the so-called CL-1 series of chemicals was born. In fact, Dr. Chen developed the pigeon-righting reflex as the basis of studying this series of "cataleptoid anesthetics." PCP had properties similar to a cataleptoid agent called bulbocapnine, a very old compound coming from a flower called Dutchman's Breeches. Dr. Chen asked Dr. Maddox to come over to the pharmacology laboratory to observe some cats which received low doses of PCP. The cats were in a state of catalepsy. One of them was sitting in this state for 24 hours. The only movement besides breathing that was observable was that of the cat's eyes moving back and forth in this sitting position. Another most unusual demonstration of the effects of PCP was in the rhesus monkey in which it was possible to give an essentially wild Indian monkey a small dose of PCP and produce serenity, tranquility and peace. Hence, the name Sernyl® and subsequently Sernylan® came about. Figure 2 demonstrates the effects of a small dose of PCP given to a wild rhesus monkey. Note that the animal is "spaced out" but relaxed and does not bite. It is remarkable how many things one can do from a surgical point of view without inducing pain. Our reaction in society today is to so control and regulate PCP that no drug company will manufacture this drug. As a result, we have lost a very good anesthetic for lower primates like monkeys that is longer acting than ketamine.

FIGURE 2

A MALE *MACACA MULATTA* MONKEY GIVEN PHENCYCLIDINE

A dose of two mg/kg i.m. phencyclidine was given about 15-30 minutes previously. Note the "spaced out" expression on the face. The monkey did not bite. When this animal was normal, it was very vicious and quite dangerous.

Just about six months after this unique demonstration of PCP effects, I was asked independently by Dr. Cal Bratton at Parke Davis to further study PCP in animals. I observed exactly what Dr. Chen had. About nine months after its synthesis in the early summer of 1957, a decision was made to do toxicity studies with PCP and (if it proved to be a safe agent) to study it in humans as a potential anesthetic. I ought to give you the information that with most general anesthetics if a

specific dose is anesthetic, twice the dose will kill. Yet in the case of PCP, a specific dose will give anesthesia but it really takes a dose 10 times or more to kill. Hence, PCP has a true advantage in improving the so-called therapeutic index; something that we all very desperately need in anesthesia even today. By the end of 1957 (almost a year later) there was approval to do clinical trials and Dr. Gajewski of Parke Davis went to Wayne State University, Department of Anesthesia. There Dr. Greifenstein and his associates were the first to give PCP to humans as an anesthetic agent. As patients were anesthetized with PCP, it became obvious that the drug, when properly administered by an anesthesiologist, was indeed very safe, far safer than most anesthetics that were then available. There was a peculiar problem that about 30 percent of the patients (unpredictably) had emergence delirium. There was the sensation of feeling no arms or legs and being in outer space. Dr. John Stirling Meyers, then head of Neurology at Wayne State University, was called in to study this phenomenon with PCP which he thought as drug-induced sensory isolation. Because of the interest of Dr. Elliot Luby (a psychiatrist at Wayne State as well as the Lafayette Clinic) in studying sensory isolation as a model of schizophrenia, he became involved with PCP research as a model psychosis. Dr. Luby asked me to consult in view of my earlier involvement in the animal work. In the late 1950s into the 1960s at least 30 Parke Davis people were assigned to making better PCP derivatives which were shorter acting, less convulsant and less delirium inducing. The motivation was, of course, to find a better anesthetic. In 1960 PCP was used as an animal anesthetic with the trade name Sernylan®. As I mentioned above, only very recently we have the sad story that Sernylan® is no longer available commercially for legitimate anesthesia of monkeys. The terms animal tranquilizer, horse tranquilizer or cow tranquilizer have always been misnomers. PCP was never any good in anesthetizing such animals. It was best in primates.

A very interesting thing is that as the phylogenetic scale is ascended, smaller and smaller doses of PCP are needed to anesthetize. The dose in the mouse is big compared to the rat, compared to the rabbit, cat, dog and even smaller in monkeys and smallest in humans. It is as though PCP becomes more potent in animals the more highly developed their cerebral cortex. In 1962 Cal Stevens, then head of Organic Chemistry at Wayne State University and a consultant to Parke Davis, made some novel ketone analogs of PCP which were tested by Dr. Duncan McCarthy at Parke Davis in monkeys. In 1963 CI 581, ketamine, was found to be the best as an anesthetic because it had less convulsant properties, was shorter acting than PCP and compared to other general anesthetics on chronic toxicity was indeed very safe. Dr. Lane of Parke Davis in 1964 contacted me and Dr. Gunter Corssen, an anesthesiologist, to do a human study. Dr. Corssen and I did the first human trials with ketamine. On August 3, 1964, ketamine was first given to humans and found to be a fantastic analgesic, anesthetic agent. It still had the property of producing an emergence delirium, but not as much as PCP itself. Ketamine produced a very unusual state of consciousness about which I talked to my wife. I mentioned to her that these ketamine-anesthetized patients were disconnected from their environment. I did not know what to call this state. Ketamine was not a classic anesthetic. Out of disconnected came "dissociative anesthetic," a term we have used ever since. In the 1970s there have been attempts to reduce the objectionable effects of ketamine in patients. Dr. Elemer Zsigmond and I have shown that after premedication with diazepam, ketamine is quite useful. Diazepam-ketamine is today clinically our best agent for anesthetizing burn patients when there are burns about the face and a mask cannot be used.

PHARMACOLOGY

The pharmacological effects of PCP are complex. The drug acts on the central nervous system. Small doses produce a drunken state with numbness of the extremities. Some species of animals are excited as are some human patients. Moderate doses are analgesic and anesthetic. The state crudely resembles sensory isolation except that sensory impulses, if one tests them electrophysiologically, reach different areas of the cortex but apparently the signals are grossly distorted. There are cataleptoid motor phenomena, including a kind of waxy rigidity. Large doses produce convulsions. This is especially true of PCP compared to ketamine. Ketamine has an advantage in that it does not produce seizures in large anesthetic doses.

Marked species differences are present. Primates and especially humans are anesthetized. Studies in animals involving drug-discrimination behavior indicate that PCP, ketamine and mixed narcotic agonists/antagonists like cyclazocine belong to a distinct class of drugs with common stimulus-generalization properties. There is also evidence of behavioral tolerance and a dependence syndrome to PCP.

PCP has important pharmacological actions insofar as the peripheral autonomic and cardiovascular systems are concerned. The compound causes an epinephrine (adrenalin) release resulting in a "fight or flight"

FIGURE 3

COMPARISON OF SYMPTOMS OF SCHIZOPHRENIA AND VARIOUS PSYCHOTOMIMETICS

Symptom	Acute Schizophrenia	Phencyclidine	Sensory Isolation	Sleep Deprivation	LSD-25
Loosening of association	++++	++	+	+	++
Overinclusive thoughts	++++	++	+	+	++
Concreteness	++	++++	+	++	+
Ambivalence	+++	++	+	+	+++
Autistic dreamy states	+++	++++	+++	++++	++++
Affect disorder	++++	+++	+	++	++
Attention disorder	+++	+++	+	+++	+++
Depersonalization	+++	++++	++	+++	+++
Feelings of influence	+++	+	+	+	+
Delusional thinking	++++	+	+	++	++
Visual hallucinations	+	+	+	++++	++++
Auditory hallucinations	++++	+	+	+	+
Withdrawal	+++	+			+
EEG changes	activated	+++	+	++++	++
Neuroleptic response	+++	+	+	+	+++
Intensified by amphetamine	+++	+	+	+	+++
Catatonia	+	++	+	+	+
Clouding of consciousness	+	+++	+	+++	++
Response to isolation	++	++	worse	+	++

reaction with an increase in heart beat, high blood pressure and a marked enhancement in the effects of substances released from sympathetic nerve endings or from the adrenal gland like epinephrine itself. There are very complex neurochemical actions as well. These include changes in a large variety of chemical messengers or neurotransmitters of which epinephrine, norepinephrine, dopamine, serotonin and acetylcholine are all involved. In addition PCP is an uncoupler of oxidative phosphorylation involving the energy mechanisms in the brain. Little wonder that PCP has such complex behavioral effects!

Recently, PCP receptors have been described in the rat brain (Zukin & Zukin 1979). What are they doing

there? Do you and I have PCP receptors? Because PCP readily binds to all kinds of materials, including glass fibers, there is a large artifactual amount of PCP binding in tissue. So the whole issue of PCP receptors in the brain needs a lot more study. If we do have PCP receptors in our brains, are they useless like an appendix or are they doing something? Are they helping to control pain?

PCP produces in humans a very complicated behavioral picture: anything from zombies to psychotics to epileptics. Dr. Luby and I compared acute schizophrenia to various drug-induced intoxications (Domino & Luby 1973). These are summarized in Figure 3. The bottom line is that PCP is our best model of schizophrenia. In fact schizophrenic patients exposed to PCP become a lot worse for a long time. Why? Why is it that one-third of humans taking PCP have a very abnormal schizophrenic-like reaction and two-thirds have no significant effect other that the transient feeling of being in outer space for a while, feeling dead for a while and feeling as though they do not have any arms or legs? Descriptions of PCP intoxication include dissociative anesthesia, schizophrenomimetic, sympathomimetic anesthesia, crystallized, cataleptoid anesthesia, body trip and outer space. Common street names for chronic phencyclidine abusers include parsley monsters, peep heads and machos (for those who can really "handle" the drug).

One of the more puzzling aspects of PCP is how it is biotransformed in the body. The important point is this: your client takes PCP but your client's liver, brain, lungs and a lot of other tissues in his/her body are converting PCP to about 15 to 20 different chemicals. There is evidence in the rat that there are at least four unknown metabolites that are present for about one week following a single dose of PCP. What are those compounds? We don't know. That's for future research. What do those compounds do? We don't know. That's also for future research. Are there specific PCP antidotes? As yet the answer is no. Finally, how can we better get rid of PCP and its metabolites? There is some evidence that making the urine more acidic facilitates the urinary concentration of PCP.

The most exciting challenge from a scientific point of view is whether or not there are PCP receptors present in the rat brain and potentially in humans. Are we merely in a dismal period of PCP abuse? Or, in fact, are we on the threshold of discovering not only something about how and why people take drugs like PCP but also something about ourselves? Will we soon learn something about ourselves that may not only make us occasionally crazy but also keep us sane? If so, then maybe the heavy price society is now paying for the harm PCP abuse causes will have a long term benefit. As one scientist who has helped "deliver" this "bastard," I hope so.

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