Penetration of pesticides in the human reproductive system. Presentation of case reports

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Introduction

Paraquat (1,1'-dimethyl-4,4-bipyridytium) is a broad spectrum contact herbicide which is highly toxic in animals and man [1, 4-7]. The toxicity of paraquat is characterized by progressive lethal pulmonary interstitial fibrosis and edema. Toxic effects on rat fetuses have been observed with paraquat [8].

The management of paraquat intoxication in a patient who is pregnant, and the effects of the ingested paraquat on the fetus, are topics that are poorly understood at present.

Since data (only animal studies) in human and unethical in vivo studies in humans are limited, we have been investigating cases of poisonings.

Data from autopsy samples of four suicides due to paraquat and organophosphates are reported. The herbicide referred to as "paraquat" in the following series is a 20% solution of 1-dimethyl-4,4 bipyridylium dichloride compound sold locally to farmers, as "Gramoxone".

Presentation of a pregnancy case (Case 1)

A 16-year-old unmarried female drank 3-4 "mouthfuls of paraquat" attempting suicide. Five minutes later she vomited 5-6 times and was transferred to the Ch.H. within 2.5 hours. A qualitative test for paraquat was strongly positive. The patient was in no distress. The laboratory data were: GOT=11 U/L, GPT=14 U/L, Ht=36%, WBC=11000/mm, PLTS=240,000/mm, Cr=1.1 mg%, pH 7.38n, PO_2=102 mmHg, PCO_2=31 mmHg, $SATO_2$=98.5%, HCO_3=26 meq/lit, Hb_sAg(-), pregnancy test positive. Specific treatment consisted of hemoperfusion (HP) using activated charcoal columns (Absorba 300, Cabro). At the same time the patient was given, manitol and magnesium sulphate through a nasogastric tube Fuller's Earth. Each hemoperfusion took 10 h and this was continued for 8 days. At the beginning, during and at the end of each hemoperfusion, blood samples were taken for the determination of paraquat in the plasma and urine. The patient improved gradually. Between the 5th and 9th day higher transaminases levels were found which later returned to normal values. The patient had extensive esopharyngal ulceration which was treated conservatively.

Sonography indicated a six-week live fetus (positive heart function). Three weeks after the paraquat ingestion and while the pregnancy was progressing regularly the patient underwent abortion with general anesthesia and as low as possible oxygen supply. Paraquat was determined in the conseptus (paraquat in tissues and fluid from the conseptus 0.25 and 0.05 μg/ml, respectively). The patient was allowed to go home on the 28th day and was examined again one and three months later. Table 1 depicts the paraquat levels during clinical treatment. At the beginning and the end of each hemoperfusion (HP) blood samples were taken for the determination of paraquat in the plasma. Every day the paraquat in the urine was evaluated (Table 1).

The levels were determined with the method of HPLC (High Pressure Liquid Chronatography).

The teratogenicity of paraquat has been in question. Traces of paraquat were seen to pass transplacentally in the mouse when large doses were given, leading to increased fetal death rate, but no specific fetal abnormalities.

Cases 2-3

A male (case 2), 43-years-old and a female (case 3), 38-years old, were found dead in the country side and in a house, respectively, by relatives. Approximate time elapsed from paraquat ingestion to death was estimated within hours. Paraquat levels in the autopsy specimens are shown in Table 2. Large quantities of paraquat (20 and 30 grams) were extracted from the stomach contents.

Case 4

A 33-year-old male, pharmacist, psychotic patient irregularly under medical treatment was admitted to the University Hospital by relatives seven hours after ingestion of about 150 ml of

Table 1. — *Paraquat levels in the plasma and urine (μg/ml) from a patient (case 1) taken before the start (a) and during (b) the hemoperfusion sessions*

Day	Plasma (a)	Plasma (b)	Urine (a)
1st	4.8	0.1-0.50	8.2
2nd	1.7	0.08-0.21	0.24
3rd	1.5	0.05-0.62	0.12
4th	1.2	0.05-0.30	0.05
5th	0.9	0.02-0.15	0.2
6th	0.8	0.025-0.10	0.02
7th	ND	ND	ND
8th	0.5	0.025	0.01

ND - Not determined

Table 2. — *Paraquat concentrations in autopsy specimens from cases 2 (*) and 3 (**) μg/g, μg/ml*

	*	**		*	**
Kidney	807	185	blood	165	73
lung	479	95	vitreous humour	45	18
liver	206	88	cerebrospinal fluid	7.4	ND
thyroid	6.4	32	urine	530	250
mid-brain	11	ND	spinal medula	9	ND
spleen	180	45	testis	21	–
epinephron	210	–	brain		16

ND - Not determined

paraquat solution. His clinical status was good; haemodynamic instability and dysponoea were not observed. A paraquat test in the urine was strongly positive. Soon after, stomach lavage with normal saline bentonite and lactusole solution was performed. Manitol and Lassix were injected intravenously for diuresis. One hour after admission, the patient started haemosorbtion-haemolysis sessions with the subclabian double-lumen catheter. Duration of the sessions: 1st - 2nd day, 12h, 3rd day, 3h (death). The procedure consisted of blood perfusion simultaneously and initially through the absorbent filter (Absorba 300, Cabro^{R}) and after through the dialyser (Cuprophan, ST15 Travenol^{R}). The patient died during therapy due to circulation collapse and multi-organ dysfunction. Paraquat levels (μg/ml) in the serum and urine before (a) and during (b) the sessions are as follows: serum 1st day 5.0 (a), 2.7 (b); 2nd day 4.7 (a), 1.7 (b); 3rd day 5.2 (a) 3.3 (b); urine 1st day 12.8 (a), 5.5 (b); 2nd day 12.5 (a), 3.2 (b); 3rd day 4.5 (a). Autopsy arterial blood paraquat level was 4.5 μg/ml. Paraquat levels in thyroid and testis autopsy specimens were 0.8 and 1.3 μg/ml, respectively.

Discussion

The data of the paraquat analysis in autopsy specimens and the case histories suggest that when large doses of paraquat solutions are ingested (100-250 ml) death results within minutes to hours depending on various factors (immediate or following vomiting, early first aid, general status of the person, clinical treatment). According to our records patients having ingested more than 100 ml were admitted to the hospital alive even 7 to 8 hours after ingestion, although the outcome was finally fatal. Proudfoot's Scherrmann's, or Hart's curves of survival and Severity Index of paraquat poisoning and Toxicological Index of paraquat could be used in most presented cases to predict the outcome of poisonings. It is also known that ingestion of small but potent amounts of paraquat may produce symptoms of poisoning 4 to 5 days later with a fatal outcome.

Case 1 is the first one of paraquat poisoning during pregnancy described in Greece and is one of the rare cases in the literature where the outcome of the fetus was not fatal. It is known that paraquat not only crosses the placenta, but is also concentrated to a level 4-6 times that of the mother [9]. The usual total outcome for the fetus suggests that it may be of value to consider early removal of the fetus by surgery in order to remove this poisonous reservoir from the mother. Rapid development of multiple organ failure is apparent in the newborn after birth in spite of the initial good Apgar score. The rapid changes in blood flow to the neonatal lung after birth enhance the active transport and accumulation of paraquat in lung tissue [1, 2]. Moreover, the fetus can be seen as a deep compartment of the mother, which results in the slow excretion of paraquat back into the maternal circulation [8].

The fetus seems to tolarate the paraquat intoxication while it is dependent on the placental circulation if it is at an early gestational age, but delivery and exposure to atmospheric concentration of oxygen, or a gestational age greater that 30 weeks, both result in rapid manifestation of the effects of paraquat poisoning. It has been suggested that the lung may be protected against pulmonary toxicity until the appearance of type II pneumonocyte activity late in gestation, at around 28 to 32 weeks [3]. Surgery and recuscitation of the infant, add to the problem of anesthesia in a situation when oxygen administration is contraindicated.

Data from an extensive study with samples from humans with occupational exposure to such substances and a correlation of these results with fertility and other similar problems is needed.

References

[1] Bus J., Gibson J.: "Postnatal toxicity of chemically administered paraquat in mice and interaction with oxygen and bromobenzene". *Toxicol. Appl. Pharmacol.*, 1975, *33*, 461.

[2] Daldrup T., Fowinkel C.: "Determination of substances using the known addition technique in forensic and clinical toxicology". Proceed. 29th Intern. Meeting Forensic Toxicol. (TIAFT), 1991, 379.

[3] Gaudreault P., Karl P., Friedman P.: "Paraquat and putrescine uptake by lung slices of fetal and newborn rats". *Drug Metal. Dispos.*, 1984, *12*, 550.

[4] Gill R., Qua S., Moffat A.: "High performance liquid chromatography of paraquat and diquid in urine with rapid sample preparation involving ion-pair extraction on disposable cartridges of octadecyl silica". *J. Chromatrog.*, 1983, *255*, 483.

[5] Groes K., Martens F., Desmet K.: "Quantification of paraquat in serum by HPLC". *J. Anal. Toxicol.*, 1993, *17*, 310.

[6] Kidd H., Hartley D., Kennedy J., James R.: "Eds European Directory of Agrochemical Products". The Royal Society of Chemitry, 1988.

[7] Knepil J.: "A short, simple method for the determination of paraquat in plasma". *Clin. Chim. Acta*, 1977, *79*, 387.

[8] Moya F., Vorndiken V.: "Passage of drugs across the placenta". *Am. J. Obs. & Gynecol.*, 1962, *84*, 1778.

[9] Talbot A., Fu C.: "Paraquat intoxication during pregnancy. A report of 9 cases". *Vet. Hum. Toxicol.*, 1988, *30* (1), 12.

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