Disposition of pesticides and toxicants in the human reproductive system in cases of acute poisoning

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Summary

The aim of this study was to estimate the penetration of some of the pesticides and toxicant substances in the human reproductive system. This knowledge is valuable because of the possible adverse influence of these substances on the human reproduction system and the development of the foetus during pregnancy. The existing data is mainly concerned with the results of experimental studies on animals or epidemiological studies. Here we report data concerning the disposition of several toxic xenobiotics (pesticides and solvents) in the tissues of the human reproductive system as well as in other organs and glands. Data was collected from cases of acute poisonings and derived mostly from autopsy materials. Xenobiotics were found to penetrate sampled tissues such as the testes, ovaries, epididymis, uterus, thyroid gland, as well as other human tissues. Further studies will clarify and confirm peculiarities of the penetration of a wide range of substances in various body tissues and will be the base of the estimation of the role of these toxicants in human reproductive ability and the outcome of pregnancy in humans.

Key words: Pesticides; Toxicants; Xenobiotics; Human reproductive system.

Introduction

The relationship between xenobiotic toxicants and birth defects was discovered in the 1960s when the sedative thalidomide was found to be the causative factor in producing severe congenital malformations in more than 7,000 infants whose mothers had taken this drug during pregnancy [1]. The scientific communitiy is nowadays increasingly concerned about the health hazards and in particular the reproductive toxicity of newly developed chemicals. Although many environmental chemicals produce acute toxic effects in the body, alterations in the reproductive system are relatively latent, requiring prolonged exposure.

There is a wide range of possible reproductive effects of environmental chemicals. In the female, such effects can occur before conception, during pregnancy and after delivery. It is evident that there are several approaches to discussing potential sites of toxic action in the female. In many instances, exposure to a toxic substance during pregnancy can not only produce birth defects in the offspring, but can lead to spontaneous abortions and other adverse effects in the endocrine system of the mother. In other cases of maternal exposure to toxic substances, teratogenicity may be the only overt property of the chemical. Not surprisingly, exposure to certain environmental chemicals during pregnancy may produce a different spectrum of toxicological manifestations in comparison to exposure of non-pregnant females to the same substances. Finally, the transplacental induction of cancer by an environmental agent represents yet another consideration in the overall concern about chemicals affecting the female reproductive system. Wilson has attempted to relate the importance of chemicals to produce development abnormalities in humans [2].

The literature reveals that the existing data on toxic effects of chemicals on the reproductive organs mainly concerns studies on experimental animals or epidemiological studies. Furthermore, basic questions regarding the penetration of the various toxicants in the tissues of the reproductive system need to be specifically addressed.

This paper reports data concerning the disposition of several toxic xenobiotics such as various pesticides (organophosphates, carbamates, methyl bromide, paraquat) and solvents (methylethylketone, toluene) in organs of the human reproductive system and other tissues of the human body. This data has been collected during the past seven years from the toxicological examination of autopsy material of cases of acute lethal intoxication due to the above substances. It is known that self-poisoning by suicidal attempts are the most common cases of acute intoxication due to pesticides. A case with a lethal outcome due to accidental solvent exposure has also been encountered.

Pesticides and solvents are widely used in agriculture. On the island of Crete, thousands of people are employed in agriculture, hence they are exposed to a lot of these toxic compounds. There is a direct need for studies on the penetration and disposition of these commonly used chemicals on the human body, especially the reproductive system, in an effort to recognize possible adverse effects on fertility and fetal development. However, ethical restrictions have not allowed studies on the concentration of these compounds in humans till now. This study is an attempt to observe the level of penetration of these toxicants in the human reproductive system using mostly autopsy material from suicidal cadavers.

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Material and Methods

Sampling

All data presented concerned samples from autopsies performed either in the Department of Forensic Pathology, the University Hospital of Heraklion or in the Office of the State Medical Examiner of Crete at the Venizelion Hospital of Heraklion. All samples were immediately and properly transmitted to the Toxicology Laboratory, University of Crete and were kept in the freezer until analysis. Autopsy specimens generally included (if available), blood, cerebrospinal fluid, parts of brain, kidney, lung, liver, urine, samples from the reproductive system and other glands, such as testes, ovaries, adrenals, thyroid and the submaxillary gland, uterus and epididymis.

Analysis

Blood, urine, stomach content and liver tissue were initially screened by immunoassay techniques (Abbot TDx and ADx) for drugs, with Head Space Gas Chromatographic techniques for volatiles, various colour tests and TLC procedures for other toxic chemicals, spectrophotometric methods for enzymes and so accordingly with GC-NPD/FID or HPLC techniques [3, 4]. Confirmations were made by running samples in different GC and HPLC conditions mainly using columns of different polarity. In some cases, mass spectrometry and/or nuclear magnetic resonance spectroscopy was utilised to confirm the structure of analytes. Extraction methodologies and sample preparation depended on the specimen and the physicochemical properties of the analyte. Usually a 2 gr specimen (fluid or tissue) was analysed and the residue specimen extract was reconstituted in 0.2 ml methanol.

Results

In Tables 1, 2 and 3 we present the data obtained from autopsy specimens from the organs of the reproductive system and the other organs and glands, in addition to the blood and the liver samples. Tables 1 and 2 depict data from tissue and fluids obtained from autopsies performed on poisoned humans. While blood, liver and vitreous humor samples were available in the majority of cases, samples from reproductive organs and others were only sparingly available. Table 3 depicts data from paraquat cases, where the number of autopsies conducted for this toxicant were more than three.

The data suggests that most xenobiotics penetrate the human reproductive tissues and sometimes accumulate in concentrations higher than those found in the blood.

Table 1. — *Concentration of Fenthion (Fen), Malathion (Mal), Methidathion (Meth), Toluene (Tln), Methylethlketone (Mek), and Methylbromide (MeBr) in autopsy specimens (μg/g or μg/ml for tissues or fluids respectively).*

Specimen	Fen	Mal	Meth	Tln	Mek	MeBr
Blood	4.8	108.5	1.8	12.4	80.4	33
Liver	16.8	257.8	6.4	50.3	41.2	1.9
Adrenal	na	130.3	5.3	na	Na	3.4
Urine	10.3	na	na	3.1	35.2	na
Brain	13.8	na	1.34	80.8	110.5	na
Testes	5.8	na	0.8	14.2	45.3	2.8
Uterus	na	170.5	na	Na	na	na
Epididymis	na	na	1.3	60.3	na	1.2
Thyroid	7.1	na	na	18.4	32.1	na
Submaxillary	na	180.3	2.9	Na	39.2	na

na: not analyzed, not available.

Table 2. — *Methomyl concentrations (μg/ml) in autopsy material from our lethal cases of poisoning.*

Autopsy Material	Case 1	Case 2	Case 3	Case 4	Mean
Blood	4.8	19.1	12.8	43.2	19.8
Liver	5.6	13.2	8.1	na	9.0
Kidney	9.8	na	15.4	29.1	18.1
Brain	1.2	0.8	4.3	na	2.1
Thyroid	5.7	13.6	na	41.5	20.3
Testes	7.2	10.5	18.1	na	11.9
Epididymis	6.1	4.8	25.6	na	12.2
Ovaries	na	na	na	31.4	31.4
Adrenal	12.4	na	19.1	18.3	16.6
Submaxillary	3.4	8.5	22.9	39.1	18.5

na: not analyzed, not available.

Table 3. — *Concentrations of paraquat in autopsy material (μg/g or μg/ml for tissues or fluids, respectively).*

Specimens	Case 1	Case 2	Case 3	Case 4	Mean
Blood	165	75	38	29	76.75
Liver	206	88	45	51	97.5
Kidney	807	185	50	48	272.5
Lung	479	95	110	91	193.75
Adrenal	210	na	39	27	92
Brain	21	16	12	21	17.5
Vitreous humour	45	18	9	7	19.75
Cerebrospinal fluid	7.4	na	na	11	9.2
Testes	21	na	na	20	20.5
Epididymis	na	na	na	39	39
Uterus	na	na	28	na	28
Thyroid	64	32	17	15	32
Submaxillary	na	19	27	na	23

na: not analyzed, not available.

Discussion

The aim of this study was to estimate the penetration of some of the pesticides and solvents in the human reproductive system. Pesticides and solvents are widely used in agriculture. On the island of Crete thousands of people are employed in agriculture and are exposed to various pesticides. There are conflicting reports on the influence of these toxicants on the reproductive ability and the fetal development of animals. However, there are no reports about these effects on the human reproductive system. We are unable to directly measure these agents in the human organs due to ethical restrictions. Consequently, the existing data concerns experimental results from animals or epidemiological studies. In our study, we determined the concentrations of a number of toxicants and solvents in the organs of humans, both in the male and female reproductive system as well as in other tissues

which may have an indirect relation to the human reproductive function. As a general conclusion, the concentrations of toxicants which were examined in the human reproductive organs and glands varied significantly from lower to higher levels in comparison with the other tissues which were examined. However, the toxicants were detected in measurable levels and that indicates a significant penetration and disposition in these tissues. We also noted high concentrations of the examined xenobiotics in endocrine glands which indirectly participate in the reproductive function such as the thyroid or adrenal gland as well as in other glands such as the submaxillary glands. All these may suggest a possible implication in human reproductive functions, e.g. in the cases of infertility, in spontaneous abortions or even in teratogenicity. However these are fields of further investigation. Another point is that the concentrations of the most toxic substances such as organophosphates (fenthion and methidathion) were in general, lower in almost all the organs compared with the corresponding levels of the rest of the xenobiotics.

We have been unable to locate studies on the effects of pesticides and solvents on the human reproductive system. There are no available reports on pregnancy outcomes of women who worked in agriculture and may have been exposed to these compounds. It is not known if there is an increase in the rate of spontaneous abortions or birth defects in this population when compared to the general population or to other chemical workers.

In rat experiments, exposure to the majority of the examined pesticides and solvents at high concentrations had embryotoxic or teratogenic effects. Organophosphate pesticides have been reported to cause some maternal toxicity, but generally do not pose the same potentially adverse effects on the female reproductive system as do pesticides of the organochlorine type. Besides the acute toxic manifestations in human females exposed to organophosphate pesticides, their effects on the endocrine system remain to be clarified. The result of one study revealed that fenthion in the concentrations occurring in the environment after aerial spraying can have marked effects on the survival and reproduction of these animals for long periods after spraying [5]. In other reports with mice experiments, exposure to organophosphate insecticide had adverse effects on preimplantational development and pregnancy outcome [6]. We noted that orgonophosphates such as fenthion and methidation are deposited in quite low concentrations in the male reproductive system, e.g. testes and epididymis which ranges between 0.8 and 5.8 μg/g. However, there were no available tissues or organs of the female reproductive system for analogous measurements in women for these toxicants.

Carbamate pesticides, specifically carbaryl, can affect the release and secretion of pituitary gonadotrophins and can later alter the prolactin content in rodents. Generally, the effects of the pesticides of the carbamate type on the human female reproductive system have not been adequately investigated. We have not found reports implicating these solvents and pesticides as male reproductive toxicants. It is possible that reproductive toxicity is limited to particular compounds in high doses. Paraoxon has been found to inhibit the fertilization of mouse gametes in vitro [7]. Hirvonen *et al.* (1993) showed that malaoxon induced brain phosphoinosite turnover and changes in brain calcium levels in pregnant and nonpregnant female rats [8]. Additionally, malathion toxicity may have an influence on protein adequacy in pregnant rats [9]. We examined four cases of lethal poisoning with methomyl in humans, three males and one female. There was a high concentration of this toxicant in the ovaries (31.4 μg/ml), higher than any other tissue. The mean value of concentration in the testes was 11.9 μg/ml and in the epididymis 12.2 μg/ml, quite a bit lower than the concentration in the other glands such as the thyroid and adrenal. Similar to methomyl, another carbamate pesticide, malathion, showed to have a high disposition in the uterus (170.5 μg/g) in the one case which was examined.

As regards methyl bromide, teratogenicity studies in rats and rabbits revealed that maternal toxicity was evident for both species up to dose levels of 30 and 10 mg/kg/day. However, these studies did not lead to the conclusion that methyl bromide was foetotoxic or teratogenic to these animals up to these dose levels [10]. We found a low concentration of this pesticide in the male reproductive system, ranging from 1.2 μg/g in the epididymis up to 2.8 μg/g in the testes.

A number of studies have shown that paraquat has a constrictive effect on the ductus arteriosus in fetal rats [11, 12]. In our study, paraquat presents a mild to moderate concentration in human reproductive organs and glands ranging from 20.5 μg/g in the testes to 28 μg/g in the uterus and 39 μg/g in the epididymis.

A number of solvents, many of which are used in the synthesis of chemical products and other industrial processes, have been examined for their embryotoxicity. Of these solvents approximately a dozen have been studied extensively and only one, namely dimethyl sulfoxide, appears to have significant teratogenic properties. Dimethyl sulfoxide produces intrauterine death and growth retardation in at least one or more of the species of animals tested. It should be noted that many such solvents have been tested at teratogenic doses, but also at concentrations below these, able to cause maternal toxicity. This fact illustrates that the placental passage of certain solvents may lead to birth defects. We examined a liposoluble solvent, toluene and one watersoluble solvent, methylethyl-ketone (MEK). Both cases were autopsy specimens from males. We examined the concentration of these solvents in testes and discovered that MEK has a higher ability of disposition in this gland in comparison to toluene.

Unlike the usually well-designed toxicological assessments used for potential therapeutic drugs, detection methods for environmental hazards are often less conspicuous or non-existent. The lack of detection methods is even more disconcerting in the instances of chemi-

cally-induced reproductive hazards, since most adverse effects are not immediately recognised. Often any retrospective studies are responsible for relating chemical-induced changes in the reproductive system. Better predictive tests are required to verify the chemical-induced changes in the endocrine system of both the male and the female.

The proposal of this study was to show whether or not, in what quantities and at which rate, different xenobiotics may be deposited into the mentioned tissues. Such information would be valuable for physicians in the management of treatments of poison cases, for medical care and the prophylaxis of cases of accidental or intentional exposure to toxicants and many other reasons. For example when there is no data available on the placental transfer of toluene, the decision-making of the physician to suggest an abortion for a seriously intoxicated pregnant woman is extremely difficult. Several examples concerning thyroid glands besides the reproductive glands, may be given, to point out the inevitability of such data. Very little data concerning the disposition of xenobiotics in the human reproductive system is available in the literature. Some data concerning experimental animals should not be easily extrapolated to humans and that has been established in several studies. As the collection of such data cannot be performed on volunteers, the investigation of specimens from autopsies of intoxicated bodies is a field of further investigation.

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