Developmental Neurotoxicity Induced by Therapeutic and Illicit Drugs

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The developmental neurotoxicity of phenytoin, isotretinoin, and methamphetamine has been reviewed to illustrate effects from both therapeutic and illicit drugs to which people are exposed and which either induce or show the potential for inducing learning disabilities following in utero exposure. In each case both human and experimental animal data are presented and compared where possible. The findings point to several conclusions. First, some drugs in current use induce developmental neurotoxicity, and it cannot safely be assumed that there are not more as yet unidentified. Second, of the types of neurotoxicity induced by drugs, learning disabilities figure prominently. Third, the effects observed are dependent on both the drug’s mechanism of action and the period of brain development during which exposure occurs. Fourth, with the exception of CNS teratogens, it is not yet possible to predict which periods of brain development are the most vulnerable for the induction of learning disabilities, as seen by the different patterns of critical periods for phenytoin and isotretinoin compared to methamphetamine. Fifth, as seen with isotretinoin, existing drugs that cause developmental neurotoxicity are not the only problem; new drugs with such effects are still being introduced. Sixth, only a small fraction of the drugs currently in use have ever been examined for developmental neurotoxicity; hence, the full scope of the problem cannot even be accurately estimated based on current information. It is concluded that prevention of new cases caused by drugs such as isotretinoin should be a high priority for future regulatory action. — Environ Health Perspect 102(Suppl 2):145-153 (1994).

Key words: developmental neurotoxicity, phenytoin, isotretinoin, methamphetamine, behavioral teratogenicity of drugs

Introduction

The purpose of this paper, as the title implies, is to review evidence that there are established examples of both therapeutic and illicit drugs that induce prenatal neurotoxicity. While suspicions about such effects have been gathering for many years, a more complete link between specific drugs and developmental neurotoxicity which extends from experimental animals to humans has only emerged in the last 15 years.

Rather than present a list of all the drugs proven or suspected of inducing developmental neurotoxicity, I have selected three examples that illustrate what I believe to be the most common pattern by which this kind of finding is revealed. The pattern begins with clinical case reports, in which a small number of cases are identified, and the suggestion is made that the effects seen in the affected children are related to a particular intrauterine drug exposure. Next, experimental animal research tests this hypothesis. In the cases presented below, such data showed a direct cause-effect relationship in animals between the drug in question and various neurological and behavioral abnormalities in the offspring. The animal data also usually establish dose-effect and exposure-effect relationships, provide control over potential confounding factors such as undernutrition and changes in postnatal rearing environment, identify sites of brain injury, and ultimately, uncover mechanisms of drug action.

Following the studies in experimental animals, the final phase is the conduct of epidemiologic studies in humans. These are usually prospective and are controlled by matching comparison subjects to cases and by using statistical methods of adjustment for covariates known or suspected to be confounders. Epidemiologic studies are not necessarily triggered by the animal experimental studies, but they nevertheless constitute the culmination of a process that when positive, implicates the drug in question to adverse effects. This, of course, is an idealized three-step process, and it seldom runs true to course. Nevertheless, it fits sufficiently well to use it to provide structure to this review.

The three drugs I have selected for review are the anticonvulsant phenytoin (Dilantin), the antiacne drug isotretinoin (Accutane), and, for the illicit drug example, the centrally acting stimulant methamphetamine (street names rock, ice, meth, or speed).

The Drugs and Their Actions

Phenytoin

Phenytoin is associated with the fetal hydantoin syndrome (FHS). FHS was first described by Hanson and Smith in 1975 (1). This was not the first time an anticonvulsant drug had been linked to developmental toxicity, that had first been suggested by Meadow (2), who suggested a link between anticonvulsants, including phenytoin, and certain congenital malformations. However, Hanson and Smith (1) were the first to suggest a syndrome associated with hydantoin exposure and the first to suggest that an integral part of the syndrome was a neurotoxic effect. The features Hanson and Smith (1) described for FHS involve the CNS including developmental delay and mild mental subnormality; craniofacial structures, including midfacial hypoplasia, hypertelorism, flattened philtrum, and shortened nose; growth effects, in this case growth retardation; and limb development, including distal phalangeal hypoplasia and small nails.

It is important to note that FHS did not occur in isolation. The fetal alcohol syndrome had been described just 2 years earlier by the same group, and in 1975 this group also described a fetal trimethadione syndrome (3). Actually, their paper was predated by a paper by Hill et al. (4), although the effects described by Hill et al.
were not characterized as a syndrome per se. Shortly thereafter, a possible fetal barbiturate syndrome was described (5). Subsequent reports were to describe a fetal primidone syndrome (6), a fetal valproate syndrome (7), and most recently a fetal carbamazepine syndrome (8).

Following the initial case reports of FHS, a series of experimental animal investigations were published. These may generally be categorized as of two types. First were those attempting to link phenytoin to congenital malformations. I will not review those here. Second were those attempting to link phenytoin to developmental neurotoxicity; I will highlight some of these.

The investigators in this area approached the issue of possible developmental neurotoxic effects from a perspective of trying to eliminate the concomitant influence of malformations on the exposed progeny. This was done to more clearly determine if there were CNS effects of intrauterine phenytoin exposure that were separate and distinct from those attributable to dysmorphogenesis of major organ systems. Therefore, these experiments administered phenytoin at subteratogenic doses.

Only those neurotoxic effects seen in the offspring of phenytoin treated dams that have been replicated numerous times will be presented here. During early postnatal development, rats exposed to phenytoin in utero exhibit heightened locomotor movement, primarily pivoting. This is illustrated in Figure 1 and is taken from Vorhees and Minck (9). The pattern is always consistent. The progeny appear normal on day 7, but become more active than controls on day 9 and subsequent days. As the progeny grow older, their hyperactivity becomes more pronounced. Figure 2 illustrates this for the same progeny as shown earlier in life in Figure 1. The apparatus is a figure-eight-shaped activity monitor; but the effect appears equally clearly in circular and square open-fields, and in hold-board chambers. Note in the right of Figure 2 that accompanying the hyperlocomotion of the phenytoin-exposed offspring is a reduced rearing frequency. Animals that amulate more, rear less. Perhaps this inverse relationship is a function of competing responses, such that rearing is crowded out of the animal’s response repertoire by the press to amulate. However, an alternative explanation is that these rats rear less because they are unstable. We later found that phenytoin-exposed animals have balance and righting reflex abnormalities that lend credence to the latter interpretation (below).

As evidence that phenytoin offspring have balance abnormalities, Elmazar and Sullivan (10) reported that rats exposed prenatally to this drug show large delays in the normal developmental acquisition of the air-righting reflex. In rats, this reflex develops rapidly during the second week of postnatal life and once attained gains additional speed during the third week of life. We have replicated Elmazar and Sullivan’s (10) air-righting effects in rats prenatally exposed to phenytoin in several experiments, one of which is illustrated in Figure 3 (11). As can be seen, regardless of the scoring criterion used, phenytoin offspring were not only delayed in the acquisition of the air-righting reflex, they never attained the speed of response seen in controls. The data in Figure 3 also include groups exposed to two other hydantoin anticonvulsants and to the inactive hydantoin core molecule itself. These other hydantoins produced no delays resembling those seen the phenytoin group. This illustrates an important point: it is risky to rely too heavily upon structure-activity relationships in making predictions about which drugs are capable of inducing developmental neurotoxicity and which ones are not.

One of the most striking effects of prenatal phenytoin is that when the offspring reach 40 to 50 days, a percentage begin to exhibit a neurological abnormality. This takes the form of excessive circling movements. It is different from the kind of circling seen in normal animals because of its speed and repetitive nature. However, it is not seen if the animal is placed in an open arena. It is most conspicuous in confined spaces where the walls are close to the animal, such as when the animal is first returned to its home cage, and in the narrow channels of a maze. Under these circumstances, the affected individuals will episodically exhibit bouts of circling in...
Figure 3. Mean proportion of animals in each group successfully righting themselves by the 2/3 (left) and the 3/3 (right) trial criterion based on visual scoring of righting by two observers. *p<0.05; **p<0.01. From Minck et al. [11]; reprinted with permission.

Figure 4. Mean (± SEM) startle amplitude (left two panels) and latency to peak response (right panel) averaged across 50 trials (25 acoustic and 25 tactile stimuli trial types). *p<0.01. From Vorhees and Minck [9].

Figure 5. Mean (± SEM) latency (sec.) to find the goal in the Morris hidden platform maze in phenytoin and control offspring under place test conditions. Extinction refers to time spent in the goal quadrant. Shift refers to relocation of the goal to the opposite quadrant. *p<0.10; *p<0.05. From Vorhees and Minck [9].
exposed offspring that do not exhibit abnormal circling (Figure 6, group PHT-N) show impaired learning, but they eventually succeed in learning the maze; the difference is that the latter animals learn at a slower rate than controls or animals exposed to other hydantoins.

To bring things full circle, consider the recent prospective study by VanOverloop et al. (16) of children exposed prenatally to phenytoin alone or in combination with one of several other anticonvulsants. They report that such children exhibit significant reductions in full-scale IQ, reduced scores on the Visual Motor Integration test, and reduced counts on a measure of locomotor activity when the children were assessed at between 4 to 8 years of age compared to controls. Controls were children identified at the same time in the study’s prospective enrollment process and were selected because they were born in one of the target hospitals with three or more minor congenital anomalies. On the verbal portion of the Wechsler tests of intelligence (WPPSI or WISC-R, depending on their age), the most affected subscales among the phenytoin-exposed children were those for Similarties and Comprehension. However, the most striking differences occurred on the performance subscales. Three performance subscales showed significant reductions in the phenytoin-exposed children: Block Design, Mazes, and Animal House Retreat. In terms of the size of the differences, the largest effect by far was on mazes, and this would appear to be the task most analogous to the animal data showing severely impaired complex maze learning. VanOverloop et al. (16) also found a number of other differences that were nearly statistically significant. Overall, their data suggest that while phenytoin-exposed children may not be at risk for mental retardation, they may be at risk for specific learning disabilities. Since approximately 0.5% of the population has epilepsy, and over 95% of epileptics are treated for their disorder with medication and phenytoin is the most widely prescribed of these medications, it stands to reason that thousands of exposed infants are born in the United States per year with the potential of phenytoin-induced learning disorders. If even 10% of those exposed prenatally to phenytoin are learning disabled, then this one anticonvulsant alone is inducing more than a thousand learning disabilities per year in the United States and thousands more in the rest of the world. While this is small from a national perspective, disabilities such as these are not only a lifelong struggle for those affected and their families, they also carry a lifetime financial burden to society. If these could be prevented by policies designed to avoid certain anticonvulsants during pregnancy, the benefits would be substantial.

Retinoids

The next example comes from the retinoids, of which vitamin A (retinol) is the most familiar. Retinol’s teratogenicity in animals has been recognized since the early 1950s, but its developmental neurotoxicity was not demonstrated experimentally until the 1970s.

In the 1980s Hoffmann-LaRoche developed a congener of retinoic acid (RA), 13-cis-retinoic acid. This compound exhibited a high degree of therapeutic efficacy for severe cystic acne, a disorder for which highly efficacious alternative treatments are not available. The company’s own preclinical animal experiments demonstrated that 13-cis-RA (isotretinoin, Accutane) was teratogenic. However, the company conducted no developmental neurotoxicity testing because it was not required by the US Food and Drug Administration (FDA).
Accordingly, the company sought FDA approval as a category X drug (contraindicated during pregnancy). The drug was approved in September 1982. Because of the nature of the laws in the United States, once the drug was on the market it could be prescribed by any physician for any purpose, not just for those purposes for which it was originally indicated. Furthermore, under current US law, the FDA has no legal authority to restrict its use. This drug, however, was not only highly efficacious for cystic acne, it was also effective for acne, and by 1985 an estimated 160,000 women of childbearing age had taken the drug. Since nowhere near this number of women has cystic acne, the obvious had happened: physicians were over-prescribing the drug. It did not take long for isotretinoin-associated malformation cases to begin to appear. In 1985, Lammer et al. (17) collected all the known retrospectively ascertained cases plus a cohort of prospectively ascertained cases. In both groups he demonstrated unequivocally a human malformation syndrome caused by isotretinoin. The affected children showed craniofacial, cardiac, thymic, and CNS malformations in those born, and increased malformations among those that never reached term. Even without these data, it was possible to predict that isotretinoin would also be a developmental neurotoxin (18). Indeed, the company could have predicted this had it attended to the scientific literature. The prediction could be based on the substantial series of already published animal experiments. I have summarized these in Table 1.

Animals exposed to retinoids during organogenesis exhibit a variety of dysfunctions in the absence of malformations, but the most reliably reported effect was a deficit in complex maze learning. Given this, it was a somber but compellingly straightforward prediction that isotretinoin-exposed children would be mentally retarded or learning disabled and further, that such effects would be seen not only among those malformed, but also among exposed children who were otherwise completely normal in appearance (18). Regrettably, this scientific prediction proved to be only too correct. Recently, Adams and Lammer (19) have completed a neuropsychological evaluation of 31 prospectively ascertained cases and a similar number of matched controls. The psychometric findings are summarized in Figure 7. As can be seen, the exposed children show a striking downward shift in their IQ distribution on the Stanford-Binet IV test of intelligence. Figure 8 shows only the isotretinoin-exposed children's IQ data

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**Figure 8.** Number of cases with malformations by IQ range and showing the relationship between major malformations and general mental ability in 5-year-old children exposed to isotretinoin in utero and controls. From Adams and Lammer (19), reprinted with permission.

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**Figure 9.** Mean ± SEM peak startle amplitude (left panel), average amplitude (center), and latency to peak response (right) averaged across 50 acoustic startle trials. * p<0.10, ** p<0.05, † p<0.01. MA, prenatal methamphetamine-treated group; Con, controls.

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**Figure 10.** Mean ± SEM maximum amplitude of the acoustic startle response averaged across test ages and trials for females. * p<0.05, ** p<0.01 compared to control. From Vorhees et al. (26, 27).
| Reference | Agent          | Strain | Exposure period, days | Function                                      | Effect |
|-----------|----------------|--------|-----------------------|-----------------------------------------------|--------|
| Malakhovskii (28,29) | Retinyl ester | Albino | 9                     | Activity                                      | ↓      |
|           |                |        |                       | Agression                                      | ↓      |
|           |                |        |                       | Active avoidance                              | ↓      |
| Butcher et al. (30) | Retinyl acetate | SD<sup>a</sup> | 8–10                  | Biel maze                                     | ↑ Errors |
| Hutchings et al. (31) | Retinol       | Wistar | 13–14<sup>b</sup>    | S<sup>r</sup>/S<sup>r</sup> Operant learning | ↓ Acquisition ↓ Extinction |
| Hutchings and Gaston (32) | Retinol       | Wistar | 16–17<sup>b</sup>    | S<sup>r</sup>/S<sup>r</sup> Operant learning | ↓ Responding |
| Vorhees (33) | Retinyl palmitate | F344  | 8–10                  | Y-Maze learning                               | ↓ Avoidance |
| Coyle and Singer (34) | Retinyl palmitate | Wistar | 8–10                  | Biel maze                                     | ↑ Errors ↑ Time |
| Vorhees et al. (35) | Retinyl palmitate | SD    | 5–7,8–10,11–13,14–16,17–19 | T-Maze learning Activity Biel maze | ↑ Time 11–13 ↑ 8–10 ↑ Errors 8–10,11–13 |
| Vorhees et al. (36) | Retinyl palmitate | SD    | 7–20                  | Cliff avoidance Surface righting Negative geotaxis Swimming ontogeny Pivoting Early activity Spontaneous alternation Biel maze Active avoidance Passive avoidance Rotorod | ↓ Performance |
| Mooney et al. (37) | Retinyl palmitate | SD    | 7–9<sup>b</sup>       | Head elevation Shoulder elevation Hindleg elevation Air righting Crawling Head pointing Cliff avoidance Rearing Wire climbing Walking Negative geotaxis Pivoting | Delayed |
| Adams (38) | Retinyl palmitate | SD    | 8–10                  | Negative geotaxis Ultrasound                 | ↑ Vocalization |
| Nolen (39) | trans-Retinoic acid | SD    | 8–10,11–13,14–16     | Negative geotaxis Auditory startle Open field activity M–maze Running wheel Active avoidance | Delayed ↑ Latency ↓ |
| Saillenfait and Vannier (40) | Retinyl palmitate | SD    | 8–20                  | Surface righting Swimming ontogeny Pupil constriction Auditory startle Negative geotaxis Open field activity Rotorod | Delayed ↓ |

*Continued*
This brings the case of isotretinoin full circle. It began with human collected case reports and a small prospective cohort in which isotretinoin’s embryopathic effects were described, then the drug’s developmental neurotoxicity was predicted based on already extant animal data, and finally its developmental neurotoxicity was proven in a human prospective study. The latter data represent, beyond any doubt, the most clear-cut human developmental neurotoxicity data ever obtained.

**Methamphetamine**

Methamphetamine (MA) is the N-methylated congener of amphetamine. Its pharmacology is the same as that of amphetamine except that MA is two to three times more potent as a CNS stimulant. Amphetamines have been abused for their neurostimulant effects for many years, but following the emergence of the free base use pattern of cocaine, it was not long before users discovered that MA could also be smoked, if it was sufficiently pure. The smoking of MA has led to a resurgence of illicit use of this drug and along with it, a concern for infants born to women using MA.

Several studies have appeared on the possible effects of MA on infants following intrauterine exposure. Three of these are worth noting. In the first, Oro and Dixon (22) described a group of infants born to women using MA, cocaine, or both. Oro and Dixon found that the stimulant group showed intrauterine growth retardation and altered neonatal behavior. The latter included lethargy, poor feeding, tremors, and abnormal sleep, among others, compared to a narcotic-exposed group or a non-drug-exposed control group. Subsequently, Dixon and Bejar (23) reported an increased incidence of intraventricular hemorrhages, echodensities, and cavitations seen on cranial ultrasonographs of stimulant-exposed infants. About one-third of the infants were exposed to MA and the remainder were exposed to cocaine or cocaine and narcotics. The abnormal sonograms were found in all stimulant-exposed groups compared to the comparison group. There were no differences in abnormal sonogram findings between infants exposed to MA and those exposed to cocaine.

**Figure 12.** Mean (± SEM) number of errors committed in the Cincinnati water maze averaged across trials. *p<0.10 compared to control. From Vorhees et al. (26,27).

| Reference          | Agent         | Strain | Exposure period, days | Function          | Effect       |
|--------------------|---------------|--------|-----------------------|-------------------|--------------|
| Kutz et al. (41)   | Retinyl acetate | SD     | 6-19                  | Pinna detachment  | Delayed      |
|                    |               |        |                       | Eye opening       | Delayed      |
|                    |               |        |                       | Incisor eruption  | Delayed      |
|                    |               |        |                       | Surface righting  |             |
|                    |               |        |                       | Cliff avoidance   |             |
|                    |               |        |                       | Grasp holding     |             |
|                    |               |        |                       | Negative geotaxis |             |
|                    |               |        |                       | Swimming ontogeny |             |
|                    |               |        |                       | Open field activity|             |
|                    |               |        |                       | S' /S' operant learning |             |

SD = Sprague-Dawley. *Dating method correct from authors’ original date so that all pregnancies are uniformly dated as evidence of conception is set equal to day zero of gestation.
In between the two reports by Dixon (22,23) and Little et al. (24) reported on 52 women and their infants exposed to MA. Little et al. reported that these infants were intraterinially growth retarded, but that no increase in birth defects occurred. They conducted no behavioral testing.

Unlike the situation with isotretinoin, the animal data available on prenatal MA were not adequate for making predictions of human developmental neurotoxicity. Therefore, we sought to improve the situation by developing a high-dose early exposure model. This was at variance with the existing published data, which were entirely devoted to a constricted portion of the dose-response range, i.e., low doses.

In one experiment, d,1-MA (50 mg/kg, twice a day) was administered to rats on days E7 to E12 of embryonic development. The offspring exhibited reduced olfactory orientation to their home-cage scent, reduced pivoting locomotion early in life, and heightened acoustic-tactile startle reactivity as weanlings. The latter may be seen in Figure 9 (25). However, when these same offspring were tested on a complex water maze, they showed no learning deficits. By comparison, rats exposed later in development to d,1-MA also exhibited heightened startle (Figure 10) and they committed more errors in a complex water maze (Figure 11) (26,27).

Note, however, that the effect on errors of commission in the complex water maze was relatively small and occurred only in those rats exposed during the second of the two exposure periods examined. More striking than this is the effect MA exposure had on the development of learning in the Morris hidden platform maze. As can be seen in Figure 12, the later-exposed group showed a significant delay both in initial learning and in learning a new goal position when the platform was shifted to another location (26,27). This shows just how sensitive the developing brain is as a function of the stage of ontogeny when the exposure occurs. It is clear that effects on learning can be induced by one drug at one stage of brain development, but at another stage by a different drug (compare phenytoin vs MA).

Discussion

The developmental neurotoxicity of three drugs has been reviewed in order to illustrate effects from both therapeutic and illicit categories of drugs to which people are exposed and which either induce or show the potential for inducing learning disabilities following in utero exposure. In each case both human and experimental animal data were presented and compared where possible. The findings point to several conclusions. First, drugs in some current use appear to induce developmental neurotoxicity; therefore, it is not correct to assume that the current pharmacopoeia of approved drugs is free of developmental neurotoxins. Second, among the types of neurotoxicity these drugs induce, learning disabilities are prominent, sometimes the most prominent, effect observed. Third, the effects observed are dependent on both the drug’s mechanism of action and the period during brain development when exposure occurs. Fourth, it is evident that simple predictions about critical periods during brain development that are most vulnerable for the induction of learning disorders are not yet possible, as seen by the different patterns of critical periods for phenytoin and isotretinoin compared to methamphetamine. Fifth, it is evident from the example of isotretinoin, that we not only face the problem of attempting to identify and correct cases of drugs already on the market that induce developmental neurotoxicity, but our society continues to introduce new developmental neurotoxins that must be uncovered. In this regard, the government’s stated position that its current testing is adequate is obviously incorrect, otherwise the isotretinoin case would never have happened. Sixth, current research expenditures only permit us to assess a small percentage of the drugs currently in use and to detect only the most serious types of developmental neurotoxicity; we know almost nothing about this aspect of toxicity for most drugs and we know even less about more subtle types of developmental neurotoxicity. This is a source of concern, because we appear to have only scratched the surface when it comes to knowing all the types of CNS damage prenatal drugs are capable of inducing.

Nevertheless, one promising avenue is now becoming feasible for dealing with some of these drug-induced problems: prevention. Most instances of developmental neurotoxicity could be prevented with current techniques of assessment if these were incorporated in preclinical testing for all drugs and other agents to which people are exposed in significant quantities. The only thing standing between us and this benefit is the Federal government. The scientific basis for regulatory action exists already. Proof of this is to be found in regulatory actions already taken by the US Environmental Protection Agency. Other agencies can follow suit anytime they choose to do so.

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