Reproductive Toxicology in Men: Drugs in Semen

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INTRODUCTION

- The incidence of congenital malformations in the overall population is 7-10%, of which chemical exposures account for 2-3%, however the source of exposure is often unclear.
- Traditionally, much research has been done on the teratogenicity of medications taken by pregnant women, as these are directly transmissible via the placenta to the conceptus, whereas men receive much less attention.
- This project aimed to determine if the semen concentrations of known teratogens could exceed concentrations of reproductive toxicological concern.

METHODOLOGY

1) **PUBMED and EMBASE literature search**: Identified a list of 10 known teratogenic drugs, including: **fluconazole, lead** (non-pharmacological xenobiotic), **isotretinoin, methotrexate, lithium carbonate, sodium valproate, carbamazepine, lamotrigine, topiramate and phenytoin.**

2) Literature review: Estimated values were identified for: therapeutic and teratogenic levels in serum and the serum: semen concentrations.

3) Web Search: Molecular weight, volume of distribution, CX LogP values are identified using web sources including Drug Bank and Electronic Medicines Compendium.

4) Calculations: Key calculations include the predicted therapeutic and teratogenic concentrations in semen, predicted [therapeutic: teratogenic] in semen, and the teratogenic threshold concentration in semen.
These are derived from:

- **Concentration = (dose x bioavailability) / volume of distribution (70kg)**
- **Predicted therapeutic or teratogenic concentration in semen = therapeutic or teratogenic concentration in serum x [semen: serum]**
- **Teratogenic threshold concentration in semen = predicted therapeutic concentration in semen / teratogenic concentration in serum.**

RESULTS

The results of the collected information from the literature and web search are shown in Table 1; the results from the key calculations are shown in Table 2, the values that are of concern are shaded in light yellow.

Drug	Therapeutic level in serum (mg/ day)	Teratogenic level in serum (mg/ day)	[Serum: semen]		Molecular weight (g/mol)	Volume of distribution (L/kg)	CX LogP
Fluconazole	200	300	9.32: 9.26	1.01	306.3	0.65	0.50
Lead	0.01	0.04	9.90: 2.10	4.71	207	Unknown	Unknown
Isotretinoin	0.50	0.50	693: 9.60	72.19	300.4	Unknown	5.66
Methotrexate	1.07	1.40	15:40	0.38	454.4	1	-1.80
Lithium carbonate	10.80	600	0.64: 1.48	0.43	73.9	0.90	0.25
Sodium valproate	1000	1000	25.90: 1.98	13.08	166.2	0.30	2.80
Carbamazepine	0.40	300	12: 6.60	1.82	236.3	1	2.80
Lamotrigine	0.01	300	10: 0.30	33.30	256.1	1.10	1.93
Topiramate	190	100	5: 3.10	1.61	339.4	0.70	0.13
Phenytoin	300	350	13.80: 2.30	6	252.3	0.75	2.47

Table 1: Literature and web search results on the therapeutic level in serum (mg/ day), teratogenic level in serum (mg/ day), [serum: semen] ratios, molecular weight, volume of distribution, CX LogP values.

	Teratogenic threshold concentration in semen	Predicted therapeutic concentration in semen (mg/L)	Predicted teratogenic concentration in semen (mg/L)	Predicted [therapeutic: teratogenic] in semen
Fluconazole	0.60	4.38	7.28	0.60
Lead	0.08	0.030	0.20	0.15
Isotretinoin	0.01	0.00021	0.00021	1
Methotrexate	3.34	0.053	0.043	1.23
Lithium Carbonate	5.38	51.21	21.99	2.33
Sodium Valproate	0.17	7	2.87	2.44
Carbamazepine	0.44	1.60	1.46	1.10
Lamotrigine	0.04	0.15	0.11	1.36
Topiramate	1.20	1.95	1.03	1.89
Phenytoin	0.36	1.70	0.79	2.15

Table 2: Calculations on teratogenic threshold concentration in semen, predicted therapeutic and teratogenic concentrations in semen and predicted [therapeutic: teratogenic] in semen.

DISCUSSION

- It is important to understand the impact of drugs in semen since it can easily be transported and exposed to the conceptus through the mother by way of transporters in the male reproductive organs.
- Particular drugs that are of concern are those in which the predicted [therapeutic: teratogenic] in semen ≥ 1.0, which means that the therapeutic levels of those drugs being consumed and passed into the semen would be nearly equal to their teratogenic levels. These include: isotretinoin, methotrexate, lithium carbonate, sodium valproate, carbamazepine, lamotrigine, topiramate and phenytoin.
- Drugs that are of concern also include those which the teratogenic threshold concentration in semen ≥ 1.0, these include: methotrexate, lithium carbonate and topiramate.
- CX LogP represents the lipophilicity of the drug, a major determining factor of the drug's absorption and distribution in the body. The drugs that are of higher concern are those which values are ≥ 1.0, as these are more lipophilic, they would be more easily dissolvable in the fatty tissues of the male reproductive organs. These drugs include: isotretinoin, sodium valproate, carbamazepine, lamotrigine and phenytoin.
- Further research needs to be done to identify whether there are common transporter molecules that are expressed in the male reproductive organs (toxicogenomic characteristics), and to determine if these predicted teratogenic concentrations would be capable of causing an increased risk of teratogenicity in humans.