

Short research communication

No increased risk of infant hypospadias after maternal use of loratadine in early pregnancy

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The original report published in 2001 on a possible association between maternal use of loratadine and an increased risk of infant hypospadias, based on data in the Swedish Medical Birth Register 1995-2001, has been followed up by continued surveillance in the same register. The original "signal" was based on 15 infants with hypospadias among 2780 loratadine-exposed infants born, representing an adjusted odd ratio of about 2.3, statistically significant. Since then another 10 cases have been identified, and 12.5 expected. For the period 2001-2004, another 1911 loratadine-exposed infants have been identified and only two had hypospadias (4 expected). Our present position is that the primary finding was a "signal" which had occurred by chance and the follow-up agrees with independent studies which indicate an absence of an association. This illustrates the care with which apparent statistically significant increases have to be handled when no prior hypothesis exists.

Key words: Hypospadias, loratadine, pregnancy, drug safety.

1. Introduction

In a recent issue of International Journal of Medical Sciences, a study was published based on a prescription register in Denmark which indicated an absence of an association between maternal use of loratadine and an increased risk for hypospadias in the offspring [1]. The reason for that study was a report we wrote [2] which described a system for an ongoing monitoring of maternal drug use and infant congenital malformations. As an example we presented the finding that maternal use of loratadine in early pregnancy was associated with a roughly doubled risk for infant hypospadias. We concluded: "The finding can still be random, but causality cannot be dismissed, even though the mechanism of action is not understood".

A reason for publishing a finding of this type is of course to encourage other scientists to look at their data sources to evaluate if the finding is supported or contradicted. Two small studies were published [3,4] which showed no such association but both were underpowered (210 and 161 women, respectively) and a study from CDC, using data from the National Birth Defects Prevention Study [5], found no association in a retrospective case-control study of 563 infants with hypospadias and 1444 male controls.

The finding also caused two experimental studies: one performed by the drug company and using rats [6] which was negative and one [7] using mice which was positive.

A further possibility to evaluate the assumed association is the continue surveillance in the original system. This we have done and present here the results.

2. Materials and Methods

Our study is - like our previous study - based on the nationwide Swedish Medical Birth Register which contains information on maternal use of drug as reported

and registered in early pregnancy [2, 8]. This information is based on interviews performed by midwives and the system has been working since July 1, 1994 which makes it possible to collect a large number of pregnancies where the women used a drug (prescription or over-the counter) and to study offspring for various characteristics, including congenital malformations. Outcome is based on the recording of the attending paediatrician. It is known that for rather mild malformations like hypospadias, recording in the Medical Birth Register is incomplete. In our previous study we supplemented the information with data from the Swedish Register of Congenital Malformations, a surveillance register to which cases of hypospadias would be reported - before 1999 only cases with the urethral orifice in or behind the coronary sulcus. In the present study, data from the Hospital Discharge Register have been added. This register contains discharge diagnoses from all inpatient care in the country. Children with hypospadias will therefore be identified also when they, perhaps years after birth, undergo reconstructive surgery. A description of the system of ascertainment of malformed infants from various sources is available [9].

We previously studied births up to and including 2001. We now supplemented those data with cases more recently identified (from the Hospital Discharge Register) and made a new study of births during 2002-2004.

Risks were estimated as risk ratios (RR) with exact 95% confidence intervals (95% CI) from exact Poisson distributions. RR was determined as the observed number of cases divided with the expected number, calculated from the total population after adjustment for year of birth, maternal age, parity, and smoking in early pregnancy.

3. Results

In the repeated analysis of the first period (up to and including 2001) we restricted births to those occurring

after July 1, 1995 and searched the registers for all known cases of hypospadias. The total number of loratadine-exposed infants is then 2780 and 25 had hypospadias identified (0.9%) - ten of the cases were thus ascertained from the Hospital Discharge Register after the neonatal period. The expected number is 12.5 and RR = 2.0 (95% CI 1.29-2.95). The risk is slightly but not significantly lower than that given in our first study (RR = 2.39, 95% CI 1.43-3.38).

For the period 2002-2004 (inclusive), we identified 1911 infants exposed to loratadine - only two had hypospadias. The expected number, calculated as above, was 4.3 and RR = 0.47 with a 95% CI 0.06-1.68).

The rates of hypospadias during the two observation periods (25 among 2780, 2 among 1911) are highly significant different ($p < 0.001$).

For the total observation period there were thus 27 cases with an expected number of 16.8, RR = 1.61, 95% CI 1.04-2.34).

4. Discussion.

This is a typical situation which arises in any kind of surveillance: a clear-cut "signal" appears which is formally statistically significant. As there is no prior hypothesis and at the surveillance process we study a large number of "exposures" (in this case drugs) and many outcomes (in this case different types of congenital malformations) it is to be expected that a number of apparently significant associations will occur. In this situation there are a number of problems: to publish or not to publish and also how such a finding should be handled by authorities.

If such a "signal" is published it is imperative to stress that in spite of formal statistical significance, the finding may be random and the reason for publishing is of course to ask other researchers to look for the presence or absence of that specific association. It is often thought that if there is a biological plausibility in the finding or if it can be repeated in animal experiments, it is more likely to be true. It should be remembered, however, that there was no biological plausibility when thalidomide was detected as a human teratogen, and animal experiments may be difficult to interpret. In the case of loratadine, both negative and positive animal findings have been published [6, 7].

New studies from independent materials are the first option. When a very strong teratogenic effect is expected it may be relatively easy to verify or reject an observation. When the "signal" refers to a rather weak effect (a 2-3 times increase in risk) and the exposure rate is not very high as was the case with loratadine, it may be very difficult to identify materials large enough and of enough quality to get meaningful information. In the example of loratadine and hypospadias, two very small studies [3, 4] which were anyway published had in fact no power whatever to detect the assumed effect of loratadine, and a larger retrospective case-control study [5] was restricted to relatively severe cases and used retrospective data on drug exposure. The most recent study [1] was based on prescription data and therefore uncertain exposure information and in spite of its size of 319 hypospadias cases found an adjusted OR for hypospadias after loratadine exposure during the first

trimester with an upper confidence limit of 10.5. The authors calculate that in order to rule out a doubling of the risk, they would need a more than four times larger material.

The next strategy, which is the basis of the present study, is continued surveillance. This necessitates the presence of an ongoing surveillance system which is the case with the Swedish Medical Birth Register. The follow-up performed gave no evidence for an association between maternal use of loratadine and hypospadias and the rate of hypospadias among loratadine-exposed infants was highly significantly lower than that during the first period. There are two possible explanations. The noticed effect of loratadine during the first period could be the result of a synergism with an unknown factor - a search for such a factor has yielded no likely candidate. The second possibility, which is much more probable, is that the first "signal" was the result of multiple testing and was therefore not repeated at follow-up.

5. Conclusion

Present evidence suggests that the earlier observed association between maternal use of loratadine in early pregnancy and birth of infants with hypospadias was the result of multiple testing.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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