Original Research

Perception of teratogenic and foetotoxic risk by health professionals: a survey in Midi-Pyrenees area

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Methods: 103 GPs and 104 CPs were interviewed. For 21 given drugs, a visual-analogue scale was used to evaluate the risk to give birth to a malformed infant if the mother had taken the drug during first trimester of pregnancy. For 9 drugs, health professionals had to say if they thought there was a potential foetotoxic and/or neonatal risk when drugs were administered during late pregnancy.

Results: 97% and 91% of GPs and CPs respectively thought that isotretinoin and thalidomide are teratogenic and more than 80% thought that amoxicillin and acetaminophen are safe in early pregnancy. However, 19% of the GPs and 33% of CPs answered there were no teratogenic risk for valproate. Around 11% of both GPs and CPs said that warfarin was safe during pregnancy. For 22% of GPs and for 13% and 27% of CPs respectively, ibuprofen and enalapril were safe on late pregnancy. For each drug, mean value of perceived teratogenic risk by health professionals was higher than values that can be found in scientific references. Concerning isotretinoin, thalidomide and metoclopramide, perceived teratogenic risk was higher for CPs.

Conclusion: These data show that the potential teratogenic and foetotoxic risk of several commonly used drugs is unknown by health professionals. Conversely, GPs and CPs who think that a risk exists, overestimate it. This misperception can lead to inappropriate decisions for pregnancy outcomes.

Keywords: Teratogens. Health Knowledge, Attitudes, Practice. France.
INTRODUCTION

After thalidomide had been marketed in the 1960s, people became aware of the teratogenic risk of drug used during pregnancy. Due to this event and several others (diethylstilbestrol in the 70s and retinoids in the 80s), drug prescription for a pregnant woman induces anxiety, not only for woman, but, also for health professionals. However, drug prescription in pregnancy is common. Prescribing or counselling drugs during pregnancy requires health professionals to assess a benefit/risk ratio not only for woman herself but also for her baby. Thus, a right evaluation of the risk is essential. A lack of knowledge of teratogenic or foetotoxic properties of a drug may enhance the risk of neonatal malformation or disease. Conversely, if the risk of malformation is underestimated, this may lead to disadvantageous decisions for the woman and her intended infant. Moreover, previous studies from our group have found differences in the perception of risks according to drugs in a same pharmacotherapeutical class or to health professionals. The aim of the present study was to evaluate the knowledge of medication risk during pregnancy of general practitioners (GP) and community pharmacists (CP) of Midi-Pyrenees area.

METHODS

General practitioners (GPs) and community pharmacists (CPs) of Midi-Pyrenees area were interviewed at the beginning of continuous courses, the subjects of which were different from drug and pregnancy. They were asked to answer individually and spontaneously to the questionnaire. All questionnaires were collected at the end of the session. Nobody refused to participate.

The questionnaire contained two parts. The first one concerned the teratogenic risk. The respondents were asked to indicate whether they think there is a risk when a given drug is taken on the first trimester of pregnancy; the possible answers were “yes”, “no” or “I don’t know”. Moreover, for each drug, health professionals were asked to put a mark along the line of a visual analogue scale (VAS) to indicate their estimation of the potential teratogenic risk of the drug. The question was: “a drug may affect formation and development of the organs of the embryo when it is taken on the first trimester of pregnancy. For each drug below, do you think there is a malformation risk? Put a harrow on the scale from 0% to 100% to indicate the value of teratogenic risk. (0%; no risk, 100%; all neonates have a birth defect”). The VAS measured 20 cm and was delimited by 2 vertical lines, from 0% (no malformation) to 100% (all the newborns were malformed). The VAS was longer than usual in order to permit a more precise evaluation of the risk value for small levels. A list of about 20 drugs was established including common medicine of different pharmacotherapeutical classes: antibiotic, analgesic, anti-inflammatory, anxiolytics, antiepileptics, antipsychotics, contraceptives, anti-emetics, anti-acid....The non proprietary name and the trade mark were given for each drug.

RESULTS

Teratogenic risk of drugs

(Table 1) The percentage of health professionals giving a positive answer about the existence of a teratogenic risk ranged from 6% for amoxicillin and acetaminophen to 97% for isotretinoin. Drugs considered as dangerous by more than 50% of health professionals were the following: isotretinoin, thalidomide, gentamicine, lithium, norfloxacine, ibuprofene, aspirine, cyproterone + ethynylestradiol, carbamazepin, warfarin, oral contraceptive and erythromycin. Acetaminophen, amoxicillin, domperidone and metoclopramide were mainly considered as safe. 11% of health professionals thought there is no risk with warfarin and 30% did not know. 26% answered that there is no risk with valproate and 23% had no idea. Nearly 17% thought that there is no risk with carbamazepine and 25% did not give an opinion. Concerning lithium, 6% answered that there is no risk and more
than 20% had no opinion, 2% and nearly 6% of health professionals had no idea about the teratogenic risk of isotretinoin and thalidomide respectively.

| Drug          | Yes (%) | No (%) | No opinion (%) | Inconsistent (%) |
|---------------|---------|--------|----------------|-----------------|
| Amoxicillin   | 63.6    | 86.0   | 2.9            | 4.6             |
| Acetaminophen | 6.3     | 87.0   | 1.0            | 5.7             |
| Domperidone   | 21.3    | 61.8   | 10.6           | 6.3             |
| Metoclopramide| 22.7    | 60.9   | 10.1           | 6.3             |
| Ranitidine    | 24.2    | 38.2   | 35.7           | 1.9             |
| Bromazepam    | 37.7    | 34.3   | 23.2           | 4.8             |
| LS COC        | 40.1    | 35.7   | 22.3           | 1.9             |
| Corticoids    | 46.9    | 32.9   | 17.4           | 2.8             |
| Valproate     | 49.8    | 26.1   | 23.7           | 0.4             |
| Erythromycin  | 50.2    | 30.0   | 17.4           | 2.4             |
| SS COC        | 51.7    | 26.1   | 20.8           | 1.4             |
| Warfarin      | 57.5    | 11.1   | 30.0           | 1.4             |
| Carbamazepine | 58.0    | 16.9   | 25.1           | 0               |
| Cyp roterone+EE| 68.2  | 12.6   | 22.7           | 1.9             |
| Aspirin       | 65.2    | 26.6   | 6.8            | 1.4             |
| Ibuprofen     | 68.6    | 20.8   | 9.2            | 1.4             |
| Norfloxacin   | 70.5    | 10.6   | 17.5           | 0.4             |
| Lithium       | 72.0    | 6.3    | 21.3           | 0.4             |
| Gentamicin    | 74.9    | 4.8    | 19.8           | 0.5             |
| Thalidomide   | 94.2    | 0      | 5.8            | 0               |
| Isotretinoin  | 97.1    | 0      | 2.4            | 0.5             |

LS COC: Low Strength combined oral contraceptives, SS COC: Standard strength combined oral contraceptives

There were statistically different responses between GPs and CPs for 12 drugs. 67% of the GPs have associated valproate with a teratogenic risk when CPs opinion is controversial (33% positive, 33% negative and 34% no idea). Concerning Bromazepam, 47% of the GPs thought there is a teratogenic risk and only 29% of the CPs had this opinion. Concerning other drugs for which there is a difference in risk knowledge (warfarin, lithium, gentamicin, norfloxacin, ibuprofen, carbamazepine, erythromycin, ranitidine, metoclopramide and domperidone), GPs generally gave more clear-cut responses than CPs ("no opinion" was more frequent for CPs: 26% for CP versus 14% for GPs).

**Risk of neonatal disease**

(Table 2) A majority of health professionals answered that codeine, aspirin, ibuprofen, warfarin and bromazepam, are not safe if they are consumed on late pregnancy and more than 90% of them thought that acetaminophen and amoxicillin are safe. However, 16%, 17% and 22% answered that there is no foetal and/or neonatal risk when aspirin, ibuprofen and enalapril are administered on late pregnancy. More than 30% of the subjects had no idea about the risk of neonatal pathology if enalapril or valproate are administered close to the end of pregnancy.

Compared to the GPs the pharmacist had a worse knowledge of neonatal risk with valproate. 62% of GPs though that valproate is not safe vs. 30% of the CPs.

**Teratogenic risk assessment**

Table 3 indicates the mean values of the perceived risk estimated by health professionals. For all drugs, the teratogenic risk was overestimated when compared to values from the literature. The estimation of the risk ranged from 13% for acetaminophen to 92% for Thalidomide. 51% of CPs did not indicate a mark on the VAS vs 19% of the GPs. When GPs and CPs are compared, the perception of teratogenic risk was statistically higher for CPs (p<0,05) for isotretinoin (CPs=94% ; GPs=85%), thalidomide (CPs=94%, GPs=90%) and metoclopramide (CPs=45%, GPs=23%).

**Table 3: Mean value of the perceived teratogenic risk by 207 healthcare professionals of Midi-Pyrenees area.**

| Drug          | Mean (SD) | Literature |
|---------------|-----------|------------|
| Aspirin       | 45.2 (4.5) | 2          |
| Acetaminophen | 13.6 (4.5) | 2          |
| Ibuprofen     | 44.5 (4.5) | 2          |
| Corticosteroids| 40.7 (4.9) | 2          |
| Erythromycin  | 50.3 (6.1) | 2          |
| Gentamicin    | 54.9 (5.4) | 2          |
| Amoxicillin   | 20.1 (8.2) | 2          |
| Norfloxacin   | 46.3 (4.7) | 2          |
| Bromazepam    | 37.6 (6.1) | 2          |
| Ranitidine    | 35.4 (5.0) | 2          |
| Metoclopramide| 28.0 (5.1) | 2          |
| Domperidone   | 24.3 (5.7) | 2          |
| SS COC        | 44.1 (7.1) | 2          |
| LS COC        | 40.6 (5.6) | 2          |
| Cyp roterone+EE| 48.8 (4.8) | 2          |
| Carbamazepine | 45.4 (4.5) | 6          |
| Valproate     | 41.8 (6.9) | 10         |
| Lithium       | 55.8 (6.4) | 12         |
| Isotretinoin  | 89.0 (5.3) | 25         |
| Warfarin      | 58.7 (5.3) | 30         |
| Thalidomide   | 91.7 (7.5) | 50         |
| LS COC: Low Strength combined oral contraceptives, SS COC: Standard strength combined oral contraceptives. A value of 2% does not differ from the rate of malformation in general population.

**DISCUSSION**

The present study evaluates teratogenic and/or fetotoxic risk perception of common medications by GPs and CPs of Midi-Pyrenees area. It shows that the potential risks for the embryo or the foetus of several commonly used drugs is unknown by a
lot of health professionals. In addition, when it is
known, teratogenic risk is overestimated.

The lack of opinion and false answers observed in
the responses to the questionnaire suggest a lack of
knowledge on drug use in pregnancy. Such a result
has already been observed by our group in an
opinion survey of CPs about drug counselling in
pregnancy. It has been shown that CPs do not
give appropriate advice to pregnant
women.1 This could be explained by several points.
First, initial training about drug use in pregnancy is
insufficient during pharmaceutical and medical
studies (2h within 6 years for CPs and 3.5h within 9
years for GPs). Moreover, some continuous
training deal with this subject but until now health
professionals are not obliged to follow these
courses. French scientific books on this topic are
few. At last, information could be misunderstood.

Health professionals overestimated the teratogenic
risk for all drugs included in our questionnaire.
Several reasons could explain this misperception.
Fear about teratogenicity appeared since
thalidomide disaster. This fear has been increased
by other events (diethylstilbestrol and retinoids) that
occurred later and were widely reported by media.
GPs and pharmacists are also afraid of litigation. On
another hand, it is possible that the mark given
graphically on the VAS does not really correspond to
the value thought by the participant. Nevertheless, a longer VAS than usually has been
chosen to better evaluate small percentages. We
also wanted to use the same methodology as a
Spanish group3 who had performed a similar study
including physicians in order to compare our results
with theirs for GPs. Moreover, even if the indicated
value on the VAS does not correspond to the real
perception of the respondent, the difference
obtained between the “true” risk and the one
estimated is so large that the conclusion remains
appropriate.

Thus, for several drugs, we compared our GPs
results with those reported in the Spanish study
where both women from the general population and
physicians (GPs, gynaecologists, students during
preclinical and clinical training) had been included.
For all these drugs, GPs of Midi-Pyrenees area
gave a higher value than the Spanish GPs. This fact
could be explained by the difference in the sample
size (25 GP in the Spanish study; 103 GP for the
present study). By chance, the Spanish group might
have included in the survey physicians who had a
better teratogenic risk perception. On the other
hand, it is possible that Spanish initial training is
more consistent on this topic. Indeed, concerning
Spanish medical students (during preclinical and
clinical training), risk perception declined as they
mature. At last, during life work, continual course,
information and communication might be better than
in France.

Disparities which were observed in responses
according to the profession or within the same
profession suggest the intervention of external
factors besides pharmacological knowledge.
Indeed, health professional opinion may be modified
by their kind of practice, training, experience,
conviction, ethic...This influence of external factors
has already been suggested in a study showing
significant differences between GPs and
pharmacists for medication use.9 In the present
study, GPs generally gave more clear-cut
responses than CPs that can be explained by the
fact that GPs have to decide to prescribe a drug or
not in a pregnant woman.

This high perception of teratogenic risk could lead to
disadvantageous decisions for pregnant women and
her intended infant. Indeed, a pregnant woman with
an acute or chronic disease could be treated
inadequately causing physiological and
psychological pain to herself and to her foetus too. If
a drug is used through inadvertence on the first
trimester, the woman could ask for pregnancy
termination all the more because women rated
teratogenic risk significantly higher than health
professionals.8,10 The fact that CPs perceive a
higher risk than it is implies that they cannot
counteract the fear that can be induced by the
information which was given by the GP to pregnant
women.

To face up this misperception of teratogenic risk
and to refresh the knowledge on medication risk
during pregnancy, the more adequate approach
could be education and continuous diffusion of
reliable information since Sanz et al. observed that
risk perception declines as medical students receive
more courses. It is also important to improve the
initial and continuous training on this field. Indeed, a
more accurate perception of the risk will permit
healthcare professionals to give better advice. It has
been shown that the tendency to terminate
pregnancy significantly decreased after an antenatal
consultation about drug exposition.11,12 Moreover,
counselling can decrease the perception of
teratogenic risk by women themselves.13 Another
point concerns the way the risk is communicated.
The ways in which risks are presented can affect
the ways in which they are perceived.15,16 Even if
a Canadian study has pointed out the difficulty of
changing the opinion despite evidence-based
facts14, the evaluation of teratogenic risk should be
carried on in the future since doubt increases risk
perception.

CONCLUSIONS

Potential teratogenic and foetotoxic risks are not
well-known by general practitioners as well as
community pharmacists. Health professionals who
think that a risk exists, overestimate it. This
misperception can lead to inappropriate decisions
for pregnancy outcomes. More efforts are needed to
sensitize general practitioners and community
pharmacists during initial and continuous trainings
and to better communicate on teratogenic risk to
inform pregnant patients.

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CONFLICT OF INTEREST
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