

More on domperidone and sudden cardiac death

French opinion leaders and regulators in the hot seat

According to *Prescrire's* evaluation of *domperidone*, it is a "drug to avoid" (1,2). In 2014 *Prescrire* published an article in which it estimated that between 25 and 120 deaths in France in 2012 were attributable to *domperidone*. The full study was then published in *Pharmacoepidemiology and Drug Safety* in 2015, with a final estimate for the year 2012 of about 230 deaths in the population aged 18 years or over (3,4). The study was led by Catherine Hill, an epidemiologist at the *Institut Gustave Roussy* (France) and, following criticisms of the findings by opinion leaders in the French media, she invited a scientific debate within the journal where the study was initially published. A year later, no scientific criticism has arrived. She has therefore decided to answer the criticisms levelled against the study in the lay media.

Dear Editors

Our paper "Estimating the number of sudden cardiac deaths attributable to the use of domperidone in France", has been criticised by the French Health Products Agency (ANSM) in the lay press (5), and by experts working for this agency (in internal papers and in a daily newspaper) (6). Our invitation to submit comments to *Pharmacoepidemiology and Drug Safety* drew no response.

To clarify the situation, we summarise below the main criticisms of our study and our responses.

The head of the French Health Products Agency presented the following arguments in *Le Figaro*: the risk is well identified, the harm-benefit balance is acceptable, and the problem lies with excessive prescribing by practitioners (5). Our comments are as follows:

He wrote: "*domperidone is highly monitored and its risks have been known for a long time*". These are recurring arguments from the authorities. The drug is "monitored", but the monitoring method used is not specified. Its risks have been known for a long time, the adverse effects are mentioned in each box, and therefore the case is closed. Patient leaflets usually list numerous adverse effects, which are always worrisome and rarely read.

He also wrote: "*when used properly, domperidone has an acceptable harm-benefit balance*". The "proper" use of domperidone is not defined. *Domperidone* is widely used to treat nausea and vomiting, symptoms for which its efficacy is considered proven, but also for conditions in which its efficacy is unproven: bloating, gastric acidity and other gastric problems in adults, gastroesophageal reflux and gastroenteritis in children, and to stimulate lactation in breast-feeding women. The EMA recommended in April 2014 "*that domperidone-containing medicines should remain*

available and may continue to be used in the EU for the management of the symptoms of nausea and vomiting (...). Domperidone will no longer be authorised to treat other conditions such as bloating or heartburn."

It would be very useful to evaluate the extent of off-label use of *domperidone* in France directly, rather than in comparison with other countries: the fact that the French use four times more *domperidone* than other populations is not a measure of the extent of its off-label use.

He concluded that the harm-benefit balance of *domperidone* is acceptable, provided its use is restricted. For whom is the harm-benefit balance acceptable: for the drug company, the drug regulatory agency, the prescriber, the patients relieved of their symptom, or the patient who died?

He also stated that *domperidone* consumption declined by 30% between 2012 and 2014, which indicates that most of its off-label use continues.

He wrote that: *domperidone* is used too widely and "*it is therefore this overconsumption that needs to be tackled*". But how else can we tackle this overconsumption than by honestly measuring the harms and benefits and publishing this information? He wrote that our estimate of 200 sudden cardiac deaths attributable to *domperidone* in France in 2012 is open to criticism, but we are still waiting for a formal written version of these criticisms, in order to provide suitably robust responses.

The safety of *domperidone* is certainly not the only drug safety problem in France. The excessive use of benzodiazepines, the continued use of third- and fourth-generation oral contraceptives and the large number of children exposed *in utero* to *sodium valproate* come to mind, but it is a very good example of an unsatisfactory situation.

Two experts from a working group of the French Health Products Agency criticised our estimates

of the excess risk, the prevalence of *domperidone* exposure, and the risk of sudden cardiac death. The first and third of these criticisms were also published in the French newspaper *Libération*, quoting one of the two experts and an anonymous "person in charge" at the French Health Products Agency (6). Some of these criticisms demonstrate an unexpectedly poor grasp of the subject.

They criticised Hondeghem et al.'s meta-analysis of the 5 studies available at the time. We used the results of this published meta-analysis at the suggestion of one of the reviewers of our paper. Any comments on the validity of this paper should be addressed to its authors.

Exposure to domperidone

These French experts criticised our estimate of the prevalence of *domperidone* exposure in France with the argument that the average age of *domperidone* users is 47.5 years (SD 19.8 years), whereas in the studies estimating the risk, the patients were older (median between 70 and 80 years).

This is a very serious mistake. The estimates of the risk include the population of users in general, therefore, the prevalence of exposure to *domperidone* in 2012 has been estimated in the adult population without cancer, using the 1/97th public sample of the French reimbursement database. If the risk were indeed limited to over 70-year-olds, the estimated risk would be much higher in this population. If we suppose that three-quarters of users are under the age of 70 years and that the risk is limited to the 25% of users over the age of 70, then a twofold risk in the total population would correspond to an eight-fold risk in the population aged 70 and over, since $\frac{3}{4} \times 0 + \frac{1}{4} \times 8 = 2$.

They also think that the 37 days we used to estimate the prevalence of

exposure is the average duration of exposure. This is another serious mistake. When estimating a relative risk by comparing risks in exposed and unexposed populations, the estimated risk depends on the definition of exposure. If the exposed population consists of anyone who ever used one tablet of *domperidone*, the relative risk will be much smaller than if it consists of individuals for whom the drug was prescribed within the previous 37 days. The 37-day period was the only definition of exposure associated with a risk estimate. It has nothing to do with duration of exposure

Risk of sudden cardiac death in France

Our estimate of 20 000 sudden cardiac deaths in France in 2012 has been criticised for being an average derived from two studies conducted in the same region, and therefore unrepresentative of the French population. However, these critics suggested no alternative strategy, other than mentioning the fact that death certificates would give the

much lower, yet probably grossly underestimated, number of 4 500 sudden cardiac deaths, plus 1 500 sudden deaths not otherwise specified. French specialists have since estimated that 23 000 to 37 000 cases of sudden death occur among adults out of hospital per year (7). We see no reason to revise our estimate.

Lastly, in *Libération* these experts stated that “for [them], the issue is to understand why 10 times more Motilium^o (*domperidone*) is used in France than in Germany” (6). Contrary to their assertion, this is most certainly not the issue. The real issue is how to reduce the use of a drug that is not very useful, slightly toxic, yet widely taken to treat symptoms that it does not alleviate. By blaming prescribers, the French Health Products Agency is shirking its responsibility. Criticising our estimate without proposing an alternative estimate is also unhelpful.

**Catherine Hill
for the authors**

.....
1- Prescrire Editorial Staff “Domperidone and cardiac disorders: avoid this neuroleptic” *Prescrire Int* 2013; **22** (144): 297.

2- Prescrire Editorial Staff “Domperidone: long trivialised, this is a drug to avoid” *Prescrire Int* 2016; **25** (175): 239.

3- Prescrire Editorial Staff “Domperidone: an indication of how many sudden deaths in France could be prevented by avoiding this low-efficacy drug” *Prescrire Analysis* 19 February 2014. english.prescrire.org. http://english.prescrire.org/Docu/DownloadDocu/PDFs/domperidone_an_indication_of_how_many_sudden_deaths.pdf

4- Hill C et al. “Estimating the number of sudden cardiac deaths attributable to the use of domperidone in France” *Pharmacoepidemiol Drug Saf* 2015; **24** (5):543-7. doi: 10.1002/pds.3771. Epub 2015 Mar 31. PMID: 25832309

5- Fréour P “La France consomme quatre fois trop de Motilium” *Le Figaro* N° 21992 23 April 2015.

6- Favereau E “Un antinauséux accusé des pires maux. Polémique. L'étude dénonçant la dangerosité du motilium est contestée” *Libération* N° 1055021 April 2015.

7- Jouven et al. “Epidémiologie de la mort subite” *La Revue du Praticien* 2015; **65**: 916-918.



Coming soon...

NEW PRODUCTS

- *Trametinib* (Mekinist^o) in metastatic or inoperable melanoma
- *Nivolumab* (Opdivo^o) in metastatic or inoperable melanoma

ADVERSE EFFECTS

- *Diethylstilbestrol* (DES): also harms the third generation
- *Mirtazapine* and *mianserin*: QT prolongation and torsades de pointes

REVIEWS

- Resectable non-small cell lung cancer
- Recommendations on pneumococcal vaccination: what evaluation has been conducted?

Outlook

- Prescrire's *Médicaments en Questions* practice improvement programme: first results