Transfer of knowledge into clinical practice: an ongoing problem. An example of adverse drug reactions impairing male fertility

Sina Vanessa Pompe,[1] Matthias Trottmann,[2] Dorothea Strobach[1]

[1]Department of Hospital Pharmacy, University Hospital Munich (LMU), Munich, Germany
[2]Department of Urology, University Hospital of Munich (LMU), Munich, Germany

Correspondence to
Dr Dorothea Strobach, Hospital Pharmacy, University Hospital of the LMU Munich, Marchioninistr 15, Munich 81377, Germany; dorothea.strobach@med.uni-muenchen.de

Received 21 October 2015
Revised 21 December 2015
Accepted 22 December 2015
Published Online First 20 January 2016

ABSTRACT

There is still a gap between the information available on the desired and adverse effects of drugs, and the use of these drugs in clinical practice. We present an enquiry from a patient with a wish to father a child. He asked if carbamazepine and/or lercanidipine might be the cause of his raised prolactin level; his urologist had denied this. After searching the literature, we found that both drugs possibly raise prolactin levels and, in addition, may have negative effects on spermatogenesis, male fertility hormones and the fertilisation process. The patient was recommended to discuss the medication with his neurologist and cardiologist and, if possible, change or discontinue both drugs. An extensive search was necessary to gather the relevant information. In this case relevant data about the drugs' effects on male fertility were available, but difficult to obtain

INTRODUCTION

An overwhelming amount of information on drugs and their desired and adverse effects is available. But, it is a challenge to use this information for an individual patient at the point of care. This is particularly the case for uncommon topics, such as drug effects on male fertility.

CASE PRESENTATION

A 32-year-old patient contacted the drug information service (DIS) asking for help with his wish to father a child. The couple had tried to conceive for about a year, and a gynaecological examination showed that his wife was fertile. The patient had been taking carbamazepine 300 mg daily for dyskinetic syndrome for 10 years and the calcium channel blocker (CCB) lercanidipine for aortic insufficiency for 3 years. He had visited an urologist, who diagnosed asthenoteratozoospermia (reduced sperm motility and amount of normal sperm morphology) and raised prolactin levels (145 µg/L; normal range 5–20 µg/L). The urologist saw no relation to the patient's drugs and recommended taking the anti-oestrogen, tamoxifen—to stimulate spermatogenesis—and intrauterine insemination. The patient was unsure about taking an additional drug and knew that a raised prolactin level could impair male fertility. He asked the DIS for more information about possible effects of his current medication on the prolactin levels.

CLINICAL QUESTION

The initial question was as follows: Do carbamazepine and/or lercanidipine alter prolactin levels? To answer this case completely, more aspects have to be considered: Are there any known effects of these drugs on spermatogenesis, sperm quality or other aspects of male fertility?

ANSWER

Search strategy

First, the summary of product characteristics (SmPC) of both drugs was searched.[1] Then, standard databases of drug information, Drugdex Drug Evaluations[2] and Facts and Comparisons,[3] were contacted. Since only sparse information was found, the search was continued in the literature database Medline and the search engine Google Scholar.

Carbamazepine

Impaired male fertility and/or abnormal spermatogenesis (reduced sperm count, motility and morphological alterations) have been reported as a rare or very rare adverse effect of carbamazepine.[1–3] Raised prolactin levels are listed as a very rare side effect.[1 4] In addition, changes in serum concentrations of male reproductive hormones have been found, including elevated sex-hormone binding globulin (normalising after discontinuation), and decreased free testosterone and dehydroepiandrosterone.[2 4] On the contrary, some studies found elevated testosterone levels during carbamazepine administration.[5] Moreover, carbamazepine may increase the hepatic clearance of thyroid hormones and inhibit the hypothalamic axis, thereby decreasing levels of free thyroxine and thyroxine-binding globulin.[2] This may lead to hypothyroidism, which is a known risk factor for male infertility.[6] There is evidence of altered pregnancy potential during carbamazepine intake in men, and successful pregnancy after discontinuation of the drug has been reported.[7]

Lercanidipine

Since lercanidipine is not licensed in all countries, only sparse or no information is found in international standard databases of drug information.[2 3] According to the German SmPC, no effects of lercanidipine on fertility are found in rats.[1] Raised prolactin levels are not reported as an adverse effect for lercanidipine in the SmPC,[1] and no report was found on searching PubMed and Google Scholar. Nevertheless, there are reports of gynaecomastia—often related to raised prolactin levels—as an adverse effect of similar CCBs.[2]

In addition, CCBs have been shown to impair sperm motility in vitro, the sperm fertilisation process and overall male fertility.[7] No studies could

To cite: Pompe SV, Trottmann M, Strobach D. *Eur J Hosp Pharm* 2016;**23**:121–122.

be found on lercanidipine, but various related agents, such as amlodipine, nifedipine and diltiazem, have been investigated. However, since the mechanism is thought to be a class effect, mediated by interaction with sperm calcium channels, available evidence on other agents of this group has to be taken into account. Successful pregnancy after discontinuation of CCBs in the male partner has been reported.[8] Furthermore, CCBs have even been discussed as potential male contraceptives.[8]

Lercanidipine is significantly metabolised via cytochrome P450 3A4, and carbamazepine is a major inducer of this isoenzyme. Thus, increased metabolism of lercanidipine has to be expected.[1]

Answer to the patient

The patient was informed that carbamazepine does very rarely cause raised prolactin levels. In addition, carbamazepine has a negative impact on spermatogenesis and might be the cause of his asthenoteratozoospermia. Moreover, alterations of important male fertility hormones can occur, including free testosterone levels in blood and thyroid hormones. Raised prolactin levels have not been reported as an adverse effect of lercanidipine, but reports on closely related agents point to a possible negative influence. More importantly, this group of drugs is known to impair sperm motility and the fertilisation process. It was found that in couples having difficulty to conceive, discontinuation of carbamazepine and CCBs by the male partner was followed by successful pregnancies.

Carbamazepine will induce a more rapid metabolism of lercanidipine and thereby diminish its effect. This information should be given to the patient's cardiologist.

The following was recommended:

- Contact the neurologist: is carbamazepine still indicated, is a dosage reduction possible or is it possible to switch to another drug?
- Contact the cardiologist: is it possible to change lercanidipine for a different antihypertensive drug? The diminished effect of lercanidipine while on co-medication with carbamazepine has to be taken into account when discussing this matter.
- Have the following checked by the urologist or general practitioner, if not already done: free testosterone level, thyroid function.
- Contact an andrologist or fertility centre for further support and control of the sperm count.

OUTCOME

The patient contacted his cardiologist who immediately changed lercanidipine to metoprolol. One month later the general practitioner found that the prolactin levels had normalised to 8.9 µg/L. The carbamazepine level was checked and found to be normal at 4.9 µg/L (target given with 4–10 µg/L). The patient had discussed carbamazepine with a neurologist, and a gradual reduction of the drug would take about 18 months until completion. A former attempt to stop carbamazepine abruptly had to be suspended owing to recurrence of symptoms. The patient contacted the DIS again, asking if metoprolol might have a negative impact on spermatogenesis and if there was a correlation between the carbamazepine dose and the negative effects on male fertility. He was informed that no negative effects of metoprolol on spermatogenesis or male fertility are to be expected, but erectile dysfunction can occur in some patients.[4 5] The patient was encouraged to ask his general practitioner for a formal report to the authorities about lercanidipine potentially causing raised prolactin levels. The patient decided that he wanted to discuss his carbamazepine treatment with a second neurologist and contact an andrologist to check his sperm count again. Some days later he reported that now normozoospermia had been found.

DISCUSSION

This case is interesting from several points of view. Most importantly, it is an excellent example of a clinical question where information is available, but not used at the point of care for a specific patient. Time, access to adequate search facilities and doubt about the existence of relevant information, have been found to be important obstacles for practitioners in searching for information.[9] This case points out that contacting a DIS is a successful way of integrating available evidence into clinical practice.

This enquiry also shows the limits of standard resources for drug information used by practitioners, especially the SmPC. The European Medicines Agency has published guidelines on the content of a SmPC, including information on fertility effects. Despite this, we recently found that only sparse, vague or no information at all was given in most SmPCs.[10] Additionally, examining the literature available on lercanidipine compared with other CCBs clearly illustrates the problems of gathering information on drugs used only in some countries. As seen in this example, the most important approach in these cases is to extend the search to closely related drugs and primary literature. Considering the time frame of lercanidipine discontinuation and prolactin level normalisation, the drug was most likely to be the cause of the raised prolactin levels in this case.

Questions about rare adverse effects are not easy to answer. This is also the case for possible drug effects on male fertility, which seem to be underestimated. However, DIS pharmacists have to ensure a more in-depth search for enquiries about rare adverse effects, and thereby find clinically relevant answers.

In addition, this case illustrates that the initial question asked often covers only part of the real clinical question. This underlines the need to always ask about all drugs taken and to consider their possible effects and interactions.

Key message

There is still a need for better integration of knowledge on adverse drug effects into clinical practice. Searching for information on drug effects on male fertility can be time consuming and demands thinking in broader terms, but can add considerable evidence to help in a clinical situation.

Contributors SVP and DS answered the drug information request and wrote the paper. MT was consulted as andrology specialist for manuscript preparation.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bundesverband der Pharmazeutischen Industrie Deutschland (editor). Summary of product characteristics online: http://www.fachinfo.de. Fachinformation Tegretal® 11/2014; Fachinformation Carmen® 03/2008 (accessed Oct 2015).
2 Drugdex Drug Evaluations (online database). Micromedex Solutions. http://www.micromedexsolutions.com (accessed Oct 2015).
3 Facts & Comparisons eAnswers (online database). Wolters Kluwer Health. https://online.factsandcomparisons.com (accessed Oct 2015).

4 Yang B, Donatucci C. Drugs that affect male sexual function. In: Mulcahy JJ. ed. *Male sexual function*. Current Clinical Urology: Humana Press, 2006:155–93.
5 Krause WKH. Drugs compromising male sexual health. Berlin-Heidelberg: Springer-Verlag, 2008.
6 Krassas GE, Pontikides N. Male reproductive function in relation with thyroid alterations. *Best Prac Res Clin Endocrinol Metab* 2004;18:183–95.
7 Brezina PR, Yunus FN, Zhao Y. Effects of pharmaceutical medications on male fertility. *J Reprod Infertil* 2012;13:3–11.
8 Triggle DJ. Calcium channel antagonists: clinical uses—past, present and future. *Biochem Pharmacol* 2007;74:1–9.
9 Ely JW, Osheroff JA, Chambliss ML, *et al*. Answering physicians clinical questions: obstacles and potential solutions. *J Am Medical Inform Assoc* 2005;12:217–24.
10 Pompe SV, Strobach D, Becker A, *et al*. Quality of information on male fertility in the summary of product characteristics—cause of concern. *Eur J Hosp Pharm* 2015;22:A86–7.