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EDITORIAL

Case Reports and Adverse Drug Reactions

Case reports—descriptions of one or more patients—used to be the most common type of publication in medical journals. Today only some journals accept case reports; these include open access journals, for example the *Journal of Medical Case Reports*. Such contributions generally illustrate some novel clinical problem or its solution.[1] Case reports are most likely to be published if they describe any of the following: 1) an unreported adverse drug reaction or interaction, 2) a new, unexpected, or unusual pattern of a disease, 3) previously unsuspected causal association between two diseases, 4) presentations, diagnosis and/or management of new and emerging diseases, 5) an unexpected association between diseases or symptoms, 6) an unexpected event in the course of observing or treating a patient, 7) findings that shed new light on the pathogenesis of a disease or an adverse effect or diagnosis, and 8) a previously unknown disease. (The unknown disease may happen quite rarely.)

In the hierarchy of evidence-based medicine, single case reports remain at the very bottom.[2] However, even a single case report can stimulate further confirmatory investigations, especially if the report goes beyond cursory observation. For example, a report of an increased incidence of leukemia within a single neighborhood can contribute to the defining characteristics of what may be an evolving disease cluster.[3]

Case reports on suspected adverse drug reaction (ADR) could also inspire subsequent systematic research that will ultimately contribute to the evidence based medicine. Any suspected ADR needs to be confirmed or refuted. Often suspected, new adverse drug reactions remain unverified; in fact, at least two reports indicate that from 26%[4] to 83%[5] of ADRs are not confirmed. Many published reports of suspected ADR are thus of limited value, because these signals are seldom investigated further. Furthermore, because this information is not incorporated consistently into drug reference sources, physicians and patients remain unaware of the potential adverse effects.[6]

In 1971, an international system for monitoring ADRs was established (WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Sweden). The database in Uppsala currently contains over three million reports of suspected ADRs. These reports use common terminologies and classifications and are supplied by physicians, qualified nurses, and pharmacists.[7] This extensive system for voluntary reporting of ADRs has a quantitative advantage (especially if patient reports are included[8]) over the case reports of ADRs published in journals, yet the case reports provide a better quality of information.

Scripta Medica publishes case reports, including those on adverse drug interactions, as well as review articles on this subject.[9] Short description of a case that would not make a full-length paper may be published as a letter to the editor. Our journal accepts these contributions as well, so long as the letter is brief and to the point.[10] The main purpose of case reports on ADRs is to stimulate vigilance and debate on this important subject.

ADRs are frequently used as examples to provide practical advanced courses in clinical pharmacology and therapeutics. The ADR case,[11] of diffuse myopathy presented here was used to stimulate discussion on drug interactions.

An 83-year-old woman presented to our clinic with a chief complaint of progressive immobilizing myopathy starting a week ago. The patient also complained of lower back pain and revealed that her urine output had sharply decreased. This patient had a history of hypercholesterolemia and had taken simvastatin (20 mg once a day) for one year. She also had hypertension and was treated with a calcium channel blocker, amlodipine (5 mg four times daily) for ten months. Because she developed edema in her lower extremities, a loop diuretic, torasemide (5 mg once daily), was added. After six months her blood pressure remained at 180/90 mmHg, so her antihypertensive therapy was changed to mibefradil[1] (50 mg once daily) one month prior to her admission. Three weeks after the change to mibefradil, the patent began experiencing muscle pain and gait disturbances. Although she has taken NSAIDs for several days, her problems have persisted.*

At the physical exam, it was found that she was unable to walk due to "functional disability" of her legs. She had a diffuse myopathy with suppressed deep-tendon reflexes. Her blood pressure was 150/80, and she had a normal body temperature. The lab data were as follows: ALT 1.179 U/L, AST 988 U/L, phosphorus 2.45 nmol/L, creatine kinase 50.125 U/ml, potassium 7,2 mmol/L, serum creatinine 814 micromol/L, urea 46,1 mmol/l]L, with myoglo-

[1] In 1998, Roche voluntarily withdraw mibefradil from the market because of its potentially harmful interactions with various drugs, especially statins. Pravastatin has a neutral drug interaction profile relative to cytochrome P450(CYP)-3A4 inhibitors (mibefradil, verapamil, itraconazole, bergamottin), but these substrates markedly increase systemic exposure to simvastatin and atorvastatin. Bergamottin, the primary furanocoumarin extracted from grapefruit juice, inhibits CYP-3A4 in liver microsomes and increases bioavailability of various drugs; a few deaths due to such food-drug interactions have been reported. Use of grapefruit during therapy with drugs that are metabolized by CYP-3A4 should be avoided.

binuria. Serum sodium, calcium and GGT were normal, and tests for HIV, hepatitis B and hepatitis C were negative. Serum levels of simvastatin and its metabolite beta-hydroxy-simvastatin acid, measured 24 hours after the last dose, were 4.95 and 1.02 ng/ml, respectively.

The following questions related to this ADR case may be discussed with students or residents: 1) What is the cause of this adverse event? and 2) How could this adverse event have been prevented? To facilitate discussion, the students and residents should read several papers, including those given in the list of references.[9-15]

In conclusion, case reports may illustrate novel clinical problems and/or their solutions. These reports are published in the medical journals. However, case reports that make some important teaching point of what is already well known but often forgotten, are now rarely published in medical journals. Instead, such contributions sometimes appear as a Letter to the Editor or among the Images in Clinical Medicine journal section. An Interesting case report, especially if it is related to the ADR, can be used as teaching material, and it may be published in the manuals or handbooks of clinical pharmacology and therapeutics.[16]

Rajko Igić
Nataša Stojaković

References

1. Fraser J. *How to publish in biomedicine—500 tips for success*, second edition. Oxford, Radcliffe Publishing, 2008.
2. Igić R, Škrbić R. *Kako se pišu i publikuju biomedicinska naučna saopštenja*. Banja Luka/Laktaši, GrafoMark, 2012.
3. Taylor RB. *The clinician's guide to medical writing*. New York, Springer, 2005.
4. Loke YK, Price D, Derry D, Aronson JK. Case reports of suspected adverse drug reactions—systematic literature survey of follow-up. *BMJ* 2006;332:5.
5. Venning GR. Validity of anecdotal reports of suspected adverse drug reactions: the problem of false alarms. *BMJ* 1982;284:249-52.
6. Loke YK. Assessing the benefit-harm balance at the bedside. *BMJ* 2004;7-8.
7. Ulfarson J, Mejyr S, Bergman U. Nurses are increasingly involved in pharmacovigilance in Sweden. *Pharmacoepidemiol Drug Saf* 2007;16:532-7.
8. Avery AJ, Anderson C, Bond CM, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technol Assess* 2011;15:1-234.
9. Kažić T. Statini—neželjena dejstva i interakcije. *Scr Med* 2011; 42:132-9.
10. Ljubojević G, Tomić N, Stojaković N. Statin-induced leg pain at night. *Scr Med* 2011;42:110.
11. Stojaković N, Igić R. Simvastatin-induced leg pain disapperas with pravastatin substitution. Srp Arh 2013 (in press).
12. Ratain M, Shepard D. Adverse drug reactions. In: *Advanced clinical pharmacology and therapeutic*s, course syllabus. Chicago, University of Chicago, 1999.
13. Jacobson RH, Wang P, Glueck CJ. *JAMA* 1997;277:296. doi:10.1001
14. Po AL, Zhang WY. What lessons can be learnt from withdrawal of mibefadil from market? *Lancet* 1998;351:1829-930.
15. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol* 2004;94:1140-6.
16. Igic R. *Praktikum iz farmakologije, toksikologije i kliničke farmakologije*. Tuzla, Medicinski fakultet, 1988.