SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Letter to the Editor

Alerts on New Restrictions in the Use of Nitrofurantoin: Do We Really Have to Be Alarmed?

Olalla Martínez-Macías[1]*, Vicente Palop-Larrea[2], Miguel Murcia-Soler[3], Virginia Pérez-Doñate[1]

[1]*Department of Microbiology, University Hospital of La Ribera, Spain*
[2]*Health Department of La Ribera, Pharmacy Health Area, Spain*
[3]*Group of Drugs of the Sociedad Española de Medicina Familiar y Comunitaria, Spain*

***Corresponding author**
Olalla Martínez-Macías, Department of Microbiology, University Hospital of La Ribera, Carretera de Alzira a Corbera Km 1, 46600 - Alzira (Valencia), Spain, Email: olmartinez@hospital-ribera.com

Submitted: 07 August 2018

Accepted: 08 August 2018

Published: 10 August 2018

ISSN: 2333-7079

Keywords

- Nitrofurantoin
- Alerts
- Adverse effects
- Urinary tract infection
- Pharmacovigilance

DEAR EDITOR

For some time, different institutions in countries such as France, the United Kingdom or the United States have published alerts reminding of the precautions that apply to the use of nitrofurantoin–an antimicrobial commonly used for the treatment of urinary infections. Specifically, in 2009 [1], the United States Food and Drug Administration (FDA) published a document describing the main characteristics of nitrofurantoin and its adverse effects at pulmonary, hepatic, neurological and hematological level, diarrhea associated to infections due to *Clostridium difficile*, etc. The Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM) in turn has published alerts since 2006 [2], on the serious adverse effects of nitrofurantoin in prolonged treatments, and more recently it issued three letters [3-5] (in 2011,2012 and 2014) alerting to the risk of serious liver and lung effects. Furthermore, the agency has offered a series of recommendations on the duration of treatment, specifying that the most serious reactions are often associated to prolonged treatments, and that such use of the drug for the prevention of recurrent urinary tract infections should be avoided. Around 2014, the short-term use of nitrofurantoin in patients with renal failure was questioned, with divergent opinions among the different drug regulatory agencies [6,7].

On the other hand, on 22 July 2016 the Spanish drug authorities (Agencia Española de Medicamentos y Productos Sanitarios [AEMPS]) published a safety note alerting to the fact that the prolonged use of nitrofurantoin has been related to serious adverse reactions of the lungs and liver, and offered recommendations for restrictive use of the drug [8].

The institutions, and particularly the AEMPS, occasionally make administrative decisions that prove difficult to interpret and which in most cases imply changes in routine clinical practice. Studies have been made on the recall of drugs destined for human use reported through the alerts of the AEMPS. Ibáñez et al., [9] conducted a retrospective descriptive study of all the alerts of the AEMPS during the period 1999-2007. They analyzed the informative notes alerting to drug recalls, based on a literature search of the adverse effects leading to such recall. The analysis compiled 18 alerts referred to drug recalls. The main reasons for recall were adverse hepatic or cardiovascular effects, and spontaneous case reporting was the main source of information. The study concluded that the information provided by these alerts is insufficient to justify the decision made, and that in most cases the references to many of the published studies are not provided. This also occurs with the alert on new restrictions in the use of nitrofurantoin–no literature reference justifying these changes being provided. Furthermore, it is notorious that different studies indicate that nitrofurantoin toxicity manifests in the context of prolonged curative and prophylactic treatments and in elderly patients [10,11], and that the incidence of serious adverse effects is low (0.001% referred to pulmonary reactions, 0.0007% for neurological reactions, 0.0003% in the case of hepatic reactions).

The Health Department of La Ribera (Valencia, Spain) has debated whether the AEMPS alert is really justified, and whether publication of the mentioned informative note conditioned prescription of this antibiotic on the part of clinicians. An analysis was made of the consumption of antibiotics and of nitrofurantoin in the period 2003-2016 in this healthcare area with a population of 250,000 inhabitants. In 2003 antibiotic use was 27.19 DDD/1000 inhabitants/day–a figure that reached 22 DDD/1000 inhabitants/day in recent years. The monthly antibiotic and nitrofurantoin consumption data remained practically constant in 2016, with a slight decrease in the months of June-July, though followed by recovery in the following months. However, nitrofurantoin use in this same period of time remained constant during the months from January to June, with a decrease in DDD/1000 inhabitants/day from July onwards (0.35 DDD/1000 inhabitants/day in June to 0.16 DDD/1000 inhabitants/day in December). Thus, in 5 months the use of nitrofurantoin showed a more than 50% decrease in DDD/1000 inhabitants/day since the alert was published on 22 July 2016.

In relation to these data, we believe that there are elements in the AEMPS alert that can generate doubts and which should be clarified and well documented. An example: "Use only for the curative treatment of cystitis, not as prophylaxis, with treatment duration of no more than 7 days". We feel that this statement is very restrictive in relation to the existing evidence and may misinterpret the use of nitrofurantoin. It is important to underscore that neither the European Medicines Agency (EMA) nor the FDA has prohibited the use of this drug for prophylactic purposes, and different reviews such as those published by the Infectious Diseases Society of America (IDSA), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) [12,13], continue to regard nitrofurantoin as a useful option when other preventive measures have failed and it is considered that the benefits of prophylaxis outweigh the low incidence of adverse effects. Nitrofurantoin is a good choice in acute urinary tract infections, administered for a maximum of 7 days. The Health Department of La Ribera reports 99% sensitivity to the drug for *Escherichia coli* – the main cause of urinary tract infections.

In conclusion, we feel it important to consider all the information emitted in relation to this alert, with a view to ensuring the best treatment decisions and not depriving patients of a tool that is very useful and accessible in certain circumstances, and which constitutes an optimum choice for managing urinary tract infections. It is important for patients to be informed about the possible adverse liver or lung symptoms, though this does not rule out nitrofurantoin as a good treatment option for acute urinary tract infections, thanks to its activity against most of the implicated pathogens – including increasingly frequent multiresistant bacteria.

REFERENCES

1. Food and Drug Administration. Macrodantin.
2. Agence nationale de sécurité du medicament et des produits de santé. Nitrofurantoïne et modifications du Résumé des Caractéristiques du Produit.
3. Agence nationale de sécurité du medicament et des produits de santé. Nitrofurantoïne et risqué de survenue d´effets indésirables hépatiques et pulmonaires lors de traitements prolongés.
4. Agence nationale de sécurité du medicament et des produits de santé. Nitrofurantoïne. Restriction d´ utilization en raison d´un risqué de survenue d´effets indésirables graves hépatiques el pulmonaires.
5. Agence nationale de sécurité du medicament et des produits de santé. Furadantine® 50 mg gélule (nitrofurantoïne): Reppels sur le bon usage – Lettre aux professionnels de santé.
6. Medicines and Healthcare products Regulatory Agency. Drug Safety Update. Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m2.
7. Oplinger M, Andrews CO. Nitrofurantoin contraindication in patients with a creatinine clearance below 60 ml/min: looking for the evidence. Ann Pharmacother. 2013; 47: 106-111.
8. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Nitrofurantoína (Furantoina®): nuevas restricciones de uso.
9. Ibáñez V, Morales-Olivas FJ, Rubio E. Retirada de medicamentos por motivos de seguridad en España (1999-2007). In: Wiley J & Sons, editors. Abstracts for the XXVI Congress of Spanish Society for Clinical Pharmacology, Cadiz (Spain). BCPT. 2013; 7-15.
10. Claussen K, Stocks E, Bhat D, Fish J, Rubin CD. How common are pulmonary and hepatic adverse effects in older adults prescribed nitrofurantoin? J Am Geriatr Soc. 2017; 65: 1316-1320.
11. Verheij TJ, Geerlings SE. 'Old" is not always bad. Clin Microbiol Infect. 2017; 23: 347-348.
12. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller RG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Disease. Clin Infect Dis. 2011; 52: e103-120.
13. De Cueto M, Aliaga L, Alós JI, Canut A, Los-Arcos I, Martínez JA, et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin. 2017; 35: 314-320.

Cite this article

Martínez-Macías O, Palop-Larrea V, Murcia-Soler M, Pérez-Doñate V (2018) Alerts on New Restrictions in the Use of Nitrofurantoin: Do We Really Have to Be Alarmed? J Pharmacol Clin Toxicol 6(4):1116.