Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two “challenging” case reports

Caterina Palleria, Christian Leporini, Serafina Chimirri, Giuseppina Marrazzo, Sabrina Sacchetta, Lucrezia Bruno, Rosaria M. Lista1, Orietta Staltari, Antonio Scuteri, Francesca Scicchitano, Emilio Russo

Department of Science of Health, School of Medicine, University of Catanzaro, Italy and Pharmacovigilance’s Centre Calabria Region, University Hospital Mater Domini, Catanzaro, 1Azienda Sanitaria Provinciale di Cosenza, Farmacovigilanza Territorio Paola, Italy

ABSTRACT

Introduction: Nowadays, based on several epidemiological data, iatrogenic disease is an emerging public health problem, especially in industrialized countries. Adverse drugs reactions (ADRs) are extremely common and, therefore, clinically, socially, and economically worthy of attention. Spontaneous reporting system for suspected ADRs represents the cornerstone of the pharmacovigilance, because it allows rapid detection of potential alarm signals related to drugs use. However, spontaneous reporting system shows several limitations, which are mainly related to under-reporting. In this paper, we describe two particular case reports, which emphasize some reasons of under-reporting and other common criticisms of spontaneous reporting systems. Materials and Methods: We performed a computer-aided search of Medline, PubMed, Embase, Cochrane library databases, national and international databases of suspected ADRs reports in order to identify previous published case reports and spontaneous reports about the ADRs reviewed in this paper, and to examine the role of suspected drugs in the pathogenesis of the described adverse reactions. Results: First, we reported a case of tizanidine-induced hemorrhagic cystitis. In the second case report, we presented an episode of asthma exacerbation after taking bimatoprost. Through the review of these two cases, we highlighted some common criticisms of spontaneous reporting systems: under-reporting and false causality attribution. Discussion and Conclusion: Healthcare workers sometimes do not report ADRs because it is challenging to establish with certainty the causal relationship between drug and adverse reaction; however, according to a key principle of pharmacovigilance, it is always better to report even a suspicion to generate an alarm in the interest of protecting public health.

Keywords: Asthma exacerbation, bimatoprost, cystitis, tizanidine, under-reporting

INTRODUCTION

Adverse drug reactions (ADRs) are extremely common. Edwards and Aronson[1] defined an ADR as — an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or dosage’s alteration, or withdrawal of the product".

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/0976-500X.120955

Address for Correspondence:
Emilio Russo, Chair of Pharmacology, Department of Science of Health, School of Medicine, University of Catanzaro, Italy, Via T. Campanella, 115; 88100 Catanzaro, Italy.
E-mail: erusso@unicz.it
Such reactions are currently reported by use of World Heart Organization’s Adverse Reaction Terminology (WHO-ART), which will eventually become a subset of the International Classification of Diseases. ADRs are classified into six types (with mnemonics): dose-related (Augmented), nondose-related (Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure). Timing, the pattern of illness, the results of investigations, and rechallenge can help attribute causality to a suspected ADR. Management includes withdrawal of the drug, if possible, and specific treatment of its effects. Suspected ADRs should be reported because spontaneous reporting represents the basis of drug safety surveillance.

Global drug safety depends on strong national systems that monitor the development and quality of medicines, report their harmful effects, and provide accurate information for their safe use.\[2\]

Pharmaceutical companies are required by regulatory authorities in all countries to perform clinical trials in order to prove efficacy and safety of their drugs before obtaining marketing authorization and making them widely available. Clinical trials evaluate the efficacy and toxicity of drugs; however, they do not provide information for larger, untested populations with different characteristics from the trial group (age, gender, state of health, ethnic origin). Moreover, clinical trials often lack important information about rare but serious adverse reactions, chronic toxicity, or interactions with other drugs. Therefore, the premarketing information about drugs are inevitably incomplete with regard to possible adverse reactions.\[2,3\] Drug safety must be followed by careful monitoring, which is called postmarketing surveillance. These “surveillance” activities are very important to allow the early detection of unexpected and/or serious adverse reactions. In particular, the effectiveness of national postmarketing surveillance is directly dependent on the active involvement of healthcare professionals and patients (according to the new European Pharmacovigilance legislation) in spontaneous reporting of suspected ADRs.\[1,2\]

Spontaneous reporting system for suspected ADRs represents the cornerstone of the postmarketing surveillance of drug safety or pharmacovigilance, because it allows to rapidly detect potential alarm signals related to drugs’ use through the early detection of new ADRs. Furthermore, the potential involvement of all physicians attributes to this epidemiological approach a function of indispensable “alarm,” especially in the identification of events with very low frequency.\[4-6\]

However, spontaneous reporting shows several limitations, which are mainly related to under-reporting, variable quality of the reported data and lack of information on drug exposure.\[2,7\]

Under-reporting is a major drawback of the pharmacovigilance system for several reasons including:\[6,8\]

- **Complacency** (i.e., the belief that very serious ADRs are well documented by the time a drug is marketed).
- **Insecurity** (i.e., the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction).
- **Difidence** (i.e., the belief that reporting an ADR should only be done if there is certainty that it is related to the use of a particular drug).
- **Indifference** (i.e., the belief that a single case that an individual physician might observe could not contribute to medical knowledge).
- **Ignorance** (i.e., the belief that it is only necessary to report serious or unexpected ADRs).
- **Fear of medico-legal consequences.**

**Lack of time** to complete the form diagnosis has also been forwarded as a factor associated with under-reporting.\[9\]

Among these reasons of under-reporting, the uncertainty of the potential causal relationship between drug and adverse reaction represents a major limitation for healthcare personnel in reporting events that seem to be related to drugs’ use but do not find a reasonable explanation to justify the causal relationship between drug and adverse event. In contrast, some ADRs are often reported apparently without a causal relationship. Moreover, the ADRs reporting may consider that cases and drugs for doses and route of administration are not able to justify the occurrence of the described adverse event.

In this paper, we review two cases of ADRs highlighting these issues: the first case involves an episode of tizanidine-induced hemorrhagic cystitis exemplifying an ADR in which it is difficult to find a reasonable justification to the onset of the adverse event. Tizanidine is an imidazoline derivative with activity at both spinal and supraspinal levels and it is often used as an antispastic agent when oral treatment is indicated. The exact mechanism of action has not been fully elucidated, but its pharmacodynamic effects are primarily linked to its central α2-adrenoceptor agonist properties. Tizanidine appears to act predominantly presynaptically in the spinal cord by reducing release of the excitatory amino acid glutamate and aspartate from the presynaptic terminal of spinal interneurons and it may facilitate the action of the inhibitory neurotransmitter glycine.\[10,11\]

Subsequently, we describe a case of asthma exacerbation after taking bimatoprost. This case represents a limitation for the report, because both the dosage and route of administration could not justify the onset of adverse event.

Bimatoprost is a synthetic prostamide analog, structurally related to prostaglandin F2α (PGF2α), which is efficacious
in the treatment of open-angle glaucoma, ocular hypertension, and other forms of glaucoma. It reduces intraocular pressure (IOP) by increasing the outflow of aqueous humor through the trabecular meshwork (pressure-sensitive) and uveoscleral (pressure-insensitive) routes.\textsuperscript{12,13}

**MATERIALS AND METHODS**

A computer-aided search of Medline, PubMed, Embase, Cochrane library databases, national and international databases of suspected ADRs reports (Pharmacovigilance Italian Database EudraVigilance database, and Vigibase\textsuperscript{TM}, the World Health Organization database) was performed to identify previous published case reports and spontaneous reports about cystitis episodes related to tizanidine use. A comparable search was performed in order to recognize cases of bronchial asthma exacerbation secondary to treatment with prostanoids, and to select relevant literature regarding the role of prostanoids in the pathogenesis of bronchial asthma. The search was performed without upper and lower limits.

Secondary search included articles cited in reference lists identified by the primary search. Records were first screened by title/abstract before full-text articles were retrieved for eligibility evaluation. Remaining articles were then subject to a citation search before a final hand-search of all reference lists. Papers were deemed eligible if they included any form of words: “tizanidine,” “bimatoprost,” “prostaglandins,” “prostanoids,” “cystitis or hematuria or renal adverse drug reactions,” “asthma attack or bronchial asthma or asthmatic form crisis or asthma exacerbation.”

All citations were downloaded into Endnote\textsuperscript{®} software version 14 (Thomson Reuters) and duplicates deleted. All articles were screened by title/abstract to determine their eligibility and then a random sample of 15\% was reviewed in order to evaluate the reliability of the selection process. In order to avoid a bias of exclusion, the full-text articles were retrieved following first round exclusions and were also subject to two independent eligibility reviews, this time with perfect agreement. The studies evaluated as eligible were enclosed in the present review. The Naranjo probability scale was used for causality attribution.

**RESULTS**

**Case report 1**

A 58-year-old female was admitted to the emergency room for hematuria. A complete blood count was performed, which showed hemoglobin of 15.3 g/dl and a white blood cells count (WBCs) of 4700/mm\textsuperscript{3}. Furthermore, hemogenic tests and urine test revealed a red blood cell carpet on urine sediment analysis. Afterwards, the patient was subjected to urological visit and ultrasonography of the urinary tract that did not evidence any current disease. The woman presented a history of gastric carcinoma with negative follow up, and was currently diagnosed with osteoporosis in advanced stage, with vertebral collapse, which was treated with risedronate 35 mg tablets (one tablet once a week). Two days before admission, the patient had undergone treatment with tizanidine (Navizan\textsuperscript{®}-Athena Pharma Italia S.r.l.) 4 mg tablets (one tablet twice daily) for lower back pain. Her medical history did not reveal either recurrent cystitis or cystitis refractory to therapy or previous urinary tract infections such as to account for the current clinical presentation. There were also no predisposing conditions that could be responsible for the onset of this adverse event. Previous history of drug or alcohol abuse and allergies were not reported.

Subsequently, tizanidine treatment was discontinued and the patient was treated with ciprofloxacin 500 mg twice a day, which resulted in improvement of the above mentioned renal adverse reaction and related symptoms. To assess the possible causal relationship between the drug and the observed adverse event (causality assessment) the Naranjo probability scale was used.

The value obtained by this algorithm was 4 indicative of a possible causal association between the suspected drug and the renal adverse reaction.

**Case report 2**

A 58-year-old female accessed hospital for acute respiratory failure secondary to asthma attack. Physical examination of the chest showed reduced breath sounds with scattered groans and wheezes, and Sp\textsubscript{O\text{2}} (arterial oxygen saturation measured by pulse oximetry) of 89\%. The patient had a history of bronchial asthma treated with short-acting \(\beta_2\)-agonist bronchodilators for about 10 years. Additionally, since 4 weeks he was taking bimatoprost 0.1 mg/ml, eye drops, solution (Lumigan\textsuperscript{®}-Allergan Pharmaceuticals Ireland) for the treatment of open-angle glaucoma. The patient was treated with intravenous corticosteroid therapy, adrenaline by aerosol and oxygen.

After hospital discharge, the patient reported what happened to her specialist ophthalmologist who diagnosed an asthmatic form crisis likely secondary to treatment with prostanoids and, therefore, decided to discontinue bimatoprost treatment.

**DISCUSSION AND CONCLUSION**

**Discussion and conclusion of Tizanidine case report**

The treatment of spasticity, a common symptom observed after pyramidal system lesion, has considerably changed during the past few years. Tizanidine is a drug that is used as a muscle relaxant. It is a centrally acting \(\alpha_2\) adrenergic agonist...
indicated for the treatment of muscle spasticity caused by different conditions such as multiple sclerosis, amyotrophic lateral sclerosis, spastic diplegia, stroke, and spinal cord injury. This imidazoline derivative is also clinically effective in the management of pain syndromes, such as pain, lower back pain, and trigeminal neuralgia. It is also prescribed off-label for migraine headaches and as an anticonvulsant. Furthermore, tizanidine has been tested as a treatment for opioid withdrawal.

Tizanidine is as effective as other antispasmodic drugs and has a better tolerability profile compared with baclofen and diazepam. The most common side-effects of tizanidine treatment include sedation, drowsiness, hypotension, dizziness, asthenia, xerostomia, muscle weakness, insomnia, hallucinations, and fatigue. Particular caution should be taken when the drug is prescribed in patients receiving concomitant therapy with antihypertensive drugs. Indeed, several case reports have shown that the addition of tizanidine in patients receiving long-term treatment with lisinopril is associated with severe hypotension and bradycardia. Moreover, clinical manifestations of tizanidine overdose include alterations of mental status, bradycardia, and hypotension. Accordingly, caution is advised when it is used in patients who have a history of orthostatic hypotension.

In addition to dry mouth, other tizanidine-induced gastrointestinal side effects include diarrhea, stomach pain, heartburn, constipation, and vomiting. Ocular side effects including blurred vision have been rarely reported, while dermatologic side effects have been isolated to rashes. Occasionally tizanidine can cause liver damage. In clinical trials, hepatic side effects associated with the use of tizanidine have included elevations of liver function tests to greater than three times the upper normal limit in 5% of patients. However, most cases of elevated liver function tests in patients receiving tizanidine rapidly resolved upon withdrawal of the medication.

Tizanidine is extensively metabolized by the liver. In particular, because tizanidine is metabolized by cytochrome P450 (CYP) 1A2, drug interaction may occur when coadministered with strong CYP1A2 inhibitors like fluvoxamine or ciprofloxacin. Both CYP1A2 inhibitors should be contraindicated for coadministration with tizanidine because it can cause serious ADRs.

The kidneys provide the final common pathway for excretion of most drugs and their metabolites, and, therefore, they are subjected to high concentrations of potentially toxic substances. Consequently, several categories of drugs can cause renal damage and their detrimental effects are increased in the presence of preexisting renal disease. In particular, the classes of drugs mainly involved in renal ADRs include: antibiotics, analgesics and nonsteroidal antiinflammatory drugs (NSAIDs). Most of nephrotoxic drugs exert a direct mechanism of cell injury; other agents can provoke renal lesions by indirect mechanisms, whose better understanding is necessary. Renal ADRs primarily occur as acute or chronic interstitial nephritis. Nephrotoxicity may be also due to drug-induced abnormalities of electrolytes or circulating metabolites: hypokalemia, hyperkalemia, hypomagnesemia, or hyperuricemia. Nephrotoxic drugs can also affect the bladder or urothelium, thus resulting in urinary retention, hemorrhagic cystitis, or carcinoma of the urinary tract. In many cases, the clinical features of drug-induced renal damage are similar to those of spontaneous renal diseases, and drugs can also exacerbate a preexisting renal failure.

Nephrotoxic drugs exposure results in renal failure occurrence depending on administered dose and several concomitant predisposing factors. Excluding acute overdose poisoning, renal failure is unpredictable in one-third of cases, while remaining cases result from therapeutic errors.

As aforementioned, both acute and chronic nephropathies may be due to a direct mechanism of drug-induced cell injury or not yet fully elucidated indirect mechanisms. In both cases, because of lack of biomoral markers for renal damage, diagnosis is difficult and it can be only performed by renal biopsy. However, physicians must be able to promptly diagnose a renal ADR; this is crucial for several reasons:

1. Mortality from drug-induced acute renal failure exceeds 12% of cases.
2. Drug-induced acute interstitial nephritis may evolve in chronic damage if the acute event does not completely revert.

Based on spontaneous reports of suspected ADRs collected in the Pharmacovigilance Italian Database (National Network of Pharmacovigilance, Rete Nazionale di Farmacovigilanza, RNF) between 2001 and 2008, renal ADRs accounted for 2% of all reports and their seriousness was much greater than the average of all ADRs (51% versus 30%). The first 20 drugs associated with serious suspected renal ADRs accounted globally for 29% of renal ADRs reports, suggesting a greater heterogeneity of potentially nephrotoxic medications. The drugs most frequently associated with these adverse reactions were diclofenac and nimesulide. Other drugs involved in nephrotoxic event were acetaminophen, acetylsalicylic acid, and ketorolac among antiinflammatory drugs; ciprofloxacin, levofloxacin, and amoxicillin among antibiotics; simvastatin and atorvastatin among statins. Cisplatin and oxaliplatin were the most represented antiblastic drugs.

To the best of our knowledge, no previous case reports about cystitis episodes due to tizanidine use have been published in the literature. We have found that, between 2003 and 2012,
the United States Food and Drug Administration (U.S. FDA) reported 54 cases of hemorrhagic cystitis related to tizanidine use in USA. However, given the small number of reports and the absence of references in the literature or RNF database (the Italian spontaneous ADRs reporting database), this case needs a better understanding. Therefore, physicians and healthcare personnel should be aware about the possible occurrence of hemorrhagic cystitis during tizanidine treatment.

Discussion and conclusion Bimatoprost’s case report

Biologically active arachidonic acid metabolites, prostaglandins (PGs), are local mediators of a great variety of physiological and pharmacological effects. They exert a large number of pharmacological actions including constriction or dilation of vascular smooth muscle cells, inducing labor, regulations of inflammatory processes and calcium movements, aggregation or disaggregation of platelets, control of cell growth, sensitization of neurons to pain, control of hormone release, wall to inhibition of acid secretion in the stomach, increase of glomerular filtration rate and action on thermoregulatory center of hypothalamus to induce fever. Prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) are mainly present in the eyes. They reduce IOP, induce vasodilatation, increase vascular permeability, and cause pupil constriction. PGE2 actions in the eye are mediated by specific E-prostanoid (EP) receptors, which can be subdivided into four subtypes: EP1 through EP4, and PGF2 actions by FP receptors. EP1 and EP2 receptor subtypes are widely distributed in smooth muscle cells where they mediate contraction and relaxation responses, respectively.

On the ocular level, the EP receptors have been localized in the epithelia of the cornea, conjunctiva, lens, trabecular cells, endothelial and smooth muscles cells of blood vessels of iris, ciliary body and choroid, all the muscles fibers of the ciliary body, photoreceptors and ganglion cells, Müller cells, and nuclear layers of the retina. The FP receptor protein is expressed in the corneal epithelium, ciliary epithelium, the circular portion of ciliary muscle, iris stroma, and smooth muscle cells. All these agents are potent FP receptor agonists.

Among these commercially available PGF2 analogues, an important therapeutic role is played by bimatoprost, a synthetic prostamide analogue (structurally related to PGF2α) that is used topically (as eye drops) to control the progression of glaucoma and in the management of ocular hypertension. It reduces IOP, increasing the outflow of aqueous fluid from eyes. When used as a 0.03% topical preparation once daily, it demonstrates sustained lowering of IOP of 7-8 mmHg over a 24-h period: treatment with topical bimatoprost 0.03% once daily for up to 48 months provided sustained reductions in IOP that were significantly greater than those with timolol 0.5% twice daily in patients with glaucoma or ocular hypertension, according to data from two large (n = 596 and 602), 12-month, phase III, randomized, double-blind trials and the extensions of these trials. In other studies it has shown greater ability to lower IOP when compared with other PG analogues. Bimatoprost also shows good IOP reduction when used in combination with other glaucoma medications.

Treatment with bimatoprost is generally well tolerated. The most common side effects include mild conjunctival hyperemia, which is generally reversible, and growth of eyelashes. Other side effects include periorbital pigmentation, discomfort, ocular surface hyperemia, and ocular pruritus. Furthermore, pharmacoeconomic data indicate that bimatoprost is cost effective in the treatment of open-angle glaucoma.

However, particular care should be taken when using this drug in patients with previous respiratory problems, as demonstrated by our case report 2 in which we have reported a special case of probably bimatoprost-induced asthma exacerbation in a patient with a history of bronchial asthma. So far, similar cases of bronchial asthma aggravation in patients on treatment with PGF2α analogues have not been reported in the literature; however, we can hypothesize that this clinical situation is related to the particular mechanism of action of PGF2α that induces an intense inflammatory reaction, vasoconstriction, and constriction of the airways through FP receptors stimulation. In fact, on the cellular level, asthmatic subjects show an increased local release of PGF2α and other inflammatory mediators by mast cells, neutrophils, eosinophils, macrophages, and lymphocytes. As a result, these substances produce an intense reaction, inflammation, and vasoconstriction.

One of the first studies to investigate the role of PGs in the pathogenesis of bronchial asthma was published over 20 years ago. Levels of prostaglandin E (PGE) and PGF2α were measured in 84 patients with asthma and compared with the levels of these PGs in nonasthmatics. A significant decrease of PGE and an increase of PGF2α were observed in asthmatic subjects.

Several studies have also looked into the influence of prostaglandin E1 (PGE1) on patients with acetylsalicylic acid-induced asthma. Acetylsalicylic acid is a cyclooxygenase...
(COX) inhibitor. Blocking COX in the arachidonic acid pathways leads to diminished levels of PGE1 and subsequent bronchoconstriction and inflammation. Administering PGE1 was found to have a protective effect on acetylsalicylic acid-induced bronchoconstriction, therefore PGE1 and its synthetic analogues (e.g., misoprostol) could be safely used in patients with asthma.[35,36]

Furthermore, significant data that could clarify the correlation between prostanoids use and asthma aggravation come from studies performed in gynecology; in fact, PGE2 and PGE1 are pharmacological agents used in obstetrics for cervical ripening and labor induction. In particular, Misoprostol is a PGE1 analogue widely used for off-label indications such as induction of abortion and of labor.[35-37]

Of note, PGF2α synthetic analogues, such as carboprost (specifically, 15-methyl-PGF2α), are also commonly used in obstetrics for their oxytocic properties and to reduce postpartum bleeding.[38]

According to the manufacturer’s drug information for the gel and the vaginal insert, PGE2 should be used with caution in patients with asthma or a history of asthma,[39] however, PGE2 and PGE1 appear to be bronchodilators.[40-42]

Moreover, in order to analyze the use of the obstetric forms of PGE2 in patients with asthma, Towers and coworkers prospectively recorded all pregnant patients that were administered PGE2 gel or suppositories over a 11-year period. A total of 189 patients with a history of asthma or active asthma were exposed to PGE2. None of the patients had any evidence of a clinical exacerbation of the disease.[43]

This study does not prove that PGE2 usage in pregnant patients with asthma is completely safe. However, from a pharmacologic point of view, in vitro studies have demonstrated that PGE2 bronchodilates pulmonary smooth muscle.[41] Therefore, in theory, the use of this agent in pregnant patients with asthma should not be concerning and could even be beneficial.

PGE1 has been found to be a strong bronchodilator in vitro and, theoretically, should not be a concern for use in pregnant patients with asthma.[35,43]

Therefore, while all drug usage in patients with asthma should be monitored carefully, asthma does not seem to be an absolute contraindication for the use of PGE2 or PGE1. In contrast, PGF2α is a potent bronchoconstrictor and probably should not be used in pregnant patients with asthma.[40]

In the light of these considerations, we can conclude that, case report 2, considering the low doses and the topical route administration of the suspected drug, it is very difficult to establish if such an adverse event, reported as an ADR, was really due to bimatoprost or whether it represented an exacerbation of the asthmatic disease secondary to viral infection or other cause.

Finally, this case report is an example of major limitation in detecting and reporting potential ADRs. In fact, physicians and other healthcare workers sometimes do not report because it is complicated to establish with certainty the correlation between drug and adverse reaction; however, according to a key principle of pharmacovigilance, it seems appropriate to point out that it is always better to report even a suspicion to generate an alarm in the interest of protecting public health.

ACKNOWLEDGMENT

The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) is kindly acknowledged for its financial and technical support.

REFERENCES

1. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. Lancet 2000;356:1233-9.
2. Mazzitello C, Esposito S, De Francesco AE, Capuano A, Russo E, De Sarro G. Pharmacovigilance in Italy: An overview. J Pharmacol Pharmacother 2013 in press.
3. World Health Organization. Safety of medicines. A Guide to Detecting and Reporting Adverse Drug Reactions. Geneva, Switzerland: World Health Organization; 2002.
4. Oshikoya KA, Awobusuyi JO. Perceptions of doctors to adverse drug reaction reporting in a teaching hospital in Lagos, Nigeria. BMC Clin Pharmacol 2009;9:14.
5. Vallano A, Cereza G, Pedrós C, Agusti A, Danés I, Aguilera C, et al. Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital. Br J Clin Pharmacol 2005;60:653-8.
6. Biagi C, Montanaro N, Buccellato E, Roberto G, Vaccheri A, Motola D. Underreporting in pharmacovigilance: An intervention for Italian GPs (Emilia-Romagna region). Eur J Clin Pharmacol 2013;69:237-44.
7. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: A systematic review. Drug Saf 2006;29:385-96.
8. Inman WH. Attitudes to adverse drug reaction reporting. Br J Clin Pharmacol 1996;41:414-5.
9. Herdeiro MT, Figueiras A, Polónia J, Gestal-Otero JJ. Physicians’ attitudes and adverse drug reaction reporting: A case-control study in Portugal. Drug Saf 2005;28:825-33.
10. De Sarro GB, De Sarro A. Antagonists of adenosine and alpha-2 adrenoceptors reverse the anticonvulsant effects of tizanidine in DBA/2 mice. Neuropsychopharmacology 1989;28:211-5.
11. Henney HR 3rd, Runyan JD. A clinically relevant review of tizanidine hydrochloride dose relationships to pharmacokinetics, drug safety and effectiveness in healthy subjects and patients. Int J Clin Pract 2008;62:314-24.
12. Curran MP. Bimatoprost: A review of its use in open-angle glaucoma and ocular hypertension. Drugs Aging 2009;26:1049-71.
13. Patil AJ, Vajaranant TS, Edward DP. Bimatoprost - a review. Expert Opin Pharmacother 2009;10:2759-68.
14. Freitag FG. Preventative treatment for migraine and tension-type headaches: Do drugs having effects on muscle spasm and tone have a role? CNS Drugs 2003;1:373-81.
15. Bou Khalil R. Tizanidine for alcohol withdrawal treatment. Med Hypotheses 2011;77:348-9.
16. Kamen L, Henney HR 3rd, Runyan JD. A practical overview of tizanidine use for spasticity secondary to multiple sclerosis, stroke, and spinal cord injury. Curr Med Res Opin 2008;24:425-39.
17. Simon O, Želnik AP. Managing spasticity with drugs. Eur J Phys Rehabil Med. 2010;46:401-10.
18. Johnson TR, Tobias JD. Hypotension following the initiation of tizanidine in a patient treated with an angiotensin converting enzyme inhibitor for chronic hypertension. J Child Neurol 2000;15:818-9.
19. Puhlow SW, Branam DL. Hypotension and bradycardia associated with concomitant tizanidine and lisinopril therapy. Am J Health Syst Pharm 2010;67:1606-10.
20. Spiller HA, Bosse GM, Adamson LA. Retrospective review of Tizanidine (Zanaflex) overdose. J Toxicol Clin Toxicol 2004;42:593-6.
21. Drug Information Online. Drugs.com. Zanaflex Side Effects. Copyright © 2000-2013 Drugs.com. [updated 2013 May 17]. Available from: http://www.drugs.com/sfx/zanaflex-side-effects.html [Last accessed on 2013 Jul 29].
22. Momo K, Homma M, Kohda Y, Ohkoshi N, Yoshizawa T, Tamaoka A. Drug interaction of tizanidine and ciprofloxacin: Case report. Clin Pharmacol Ther 2006;80:717-9.
23. Roberts RC, Part NJ, Pokorny R, Muir C, Leslie GC, Enre M. Pharmacokinetics and pharmacodynamics of tizanidine. Neurology 1994;44(11 Suppl 9):S29-31.
24. Fanos V, Mormile R, Benini D, Vecchini S, Cuzzolin L. Flurithromycin-induced acute interstitial nephritis. Pediatr Infect Dis J 2000;19:366-7.
25. Kleinknecht D, Landais P, Goldfarb B. Acute renal failure associated with drugs or iodinated contrast media. Results of a cooperative multicentric study by the Nephrology Society. Nephrologie 1986;7:41-6.
26. Available from: http://www.agenziafarmaco.gov.it/en/content/post-marketing-surveillance. Rete Nazionale di Farmacovigilanza (Pharmacovigilance National Network; last accessed 15 July 2013).
27. Beers MH, Berkow R. The merck manual of diagnosis and therapy. 17th ed. New Jersey: Whitehouse Station; 1999. p. 556-68, 1053-4.
28. Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Marrazzo G, et al. Bimatoprost ophthalmic solution 0.03% lowered intraocular pressure of normal-tension glaucoma with minimal adverse events. Clin Ophthalmol 2012;6:1547-52.
29. Beers MH, Berkow R. The merck manual of diagnosis and therapy. 17th ed. New Jersey: Whitehouse Station; 1999. p. 556-68, 1053-4.
30. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al, editors. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill; 1998. p.1419-23.
31. Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Marrazzo G, et al. Bimatoprost ophthalmic solution 0.03% lowered intraocular pressure of normal-tension glaucoma with minimal adverse events. Clin Ophthalmol 2012;6:1547-52.
32. Beers MH, Berkow R. The merck manual of diagnosis and therapy. 17th ed. New Jersey: Whitehouse Station; 1999. p. 556-68, 1053-4.
33. Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al, editors. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill; 1998. p.1419-23.
34. Sokolova TS, Reznik JB, Markov CM. Role of prostaglandins in the pathogenesis of bronchial asthma in children and possibilities in therapeutic treatment. Allergol Immunopathol (Madrid) 1984;12:267-73.
35. Szmidt M, Wasik W. The influence of misoprostol (synthetic analogue of prostaglandin E1) on aspirin-induced bronchoconstriction in aspirin-sensitive asthma. J Investig Allergol Clin Immunol 1996;6:121-5.
36. Kelsen SG, D’Alonzo GE. Acute and Chronic Effects of Misoprostol in the Control of Asthma: A Pilot Study in Five Subjects. Am J Ther 1995;2:793-8.
37. Hofmeyr GJ, Gülmezoglu AM, Pleggi C. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2010;10:CD000941.
38. Bygdeman M. Prostaglandin analogues and their uses. Baillieres Clin Obstet Gynaecol 1992;6:893-903.
39. Thomson PDR. Physician’s desk reference, 57th ed. Montvale (NJ); 2003. p. 1347-9.
40. Dombrowski MP. Physician’s desk reference, 57th ed. Montvale (NJ); 2003. p. 1347-9.
41. Dombrowski MP. Physician’s desk reference, 57th ed. Montvale (NJ); 2003. p. 1347-9.
42. Wasiak W, Szmidt M. A six week double blind, placebo controlled, crossover study of the effect of misoprostol in the treatment of aspirin sensitive asthma. Thorax 1999;54:900-4.