International Journal of Antimicrobial Agents 47 (2016) 490–494

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

High rates of off-label use in antibiotic prescriptions in a context of dramatic resistance increase: a prospective study in a tertiary hospital ☆

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ARTICLE INFO

Article history:
Received 15 February 2016
Accepted 2 April 2016

Keywords:
Off-label
Antibiotics
Marketing authorisation
Hospital

ABSTRACT

The use of antibiotics, as any other drug, is regulated by the terms of its marketing authorisation, notified in the Summary of Product Characteristics (SPC). If a prescription is not in accordance with the SPC, the physician prescribes off-label. There is very little literature regarding off-label use of antibiotics in adult healthcare facilities. A prospective monocentric study was conducted during 11 days from February to June 2015 in hospitalised patients from a tertiary teaching hospital with a high prevalence of multidrug-resistant organism colonisation to evaluate off-label use of antibiotics. Two independent experts assessed whether prescriptions complied with the latest guidelines in infectious diseases and whether off-label use of antibiotics was associated with an increased risk of adverse events. In total, 160 antibiotic prescriptions were analysed, of which 76 (47.5%) were off-label. Of the 76 off-label prescriptions, 50 (65.8%) were off-label regarding indications and 26 (34.2%) regarding doses. Nevertheless, 46/50 off-label indications (92.0%) and only 14/26 off-label doses (53.8%) were approved by experts, especially because of dose adjustment requirements. During follow-up, the rate of reported adverse events was not statistically different between patients with ($n = 76$) and without ($n = 84$) off-label prescriptions ($P = 0.35$). In a context of multidrug resistance and a lack of new drugs, high rates (47.5%) of antibiotic off-label use were observed in our hospital, but without an increased rate of adverse events. Moreover, 78.9% of off-label uses were in accordance with guidelines. Therefore, the SPC is not the warrant of an appropriate use of antibiotics.

1. Introduction

Antibiotics, as any other drug, require a marketing authorisation (MA) application that defines a regulatory framework for their use, e.g. indication, dose and administration route, which are notified in the Summary of Product Characteristics (SPC). Off-label prescription is defined by situations where a commercialised drug is used, intentionally or not, beyond the SPC specifications [1]. MA may vary between countries.

In the USA, legal authorities recognise physicians' discretion to prescribe products off-label [2]. In France, Public Health Law states that physicians should prescribe a drug in compliance with the MA [3], except for situations where no alternative treatment is available and only if scientific data support the use of this drug. In such a case, the physician in charge engages his responsibility and must inform the patient about his decision and the risks and benefits engendered by such off-label use. In the literature, ca. 50% of physicians are concerned by off-label prescription [4], which mostly occurs in paediatrics, gerontology, psychiatry and oncology departments [5]. There are very few reports regarding off-label use of antibiotics in hospitalised adults [6], mainly of a retrospective nature and regarding outpatients.

Therefore, a prospective study was conducted to evaluate off-label use of antibiotics. The aim was to evaluate whether our antibiotic prescriptions were in accordance with the MA, in an era of dramatic increase in multidrug-resistant organisms (MDROs) with sometimes deadlock situations. The objectives of this study were to sequentially evaluate (i) the rate of off-label prescriptions and whether those prescriptions complied with the latest guidelines in

☆ This work was presented in part at the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 17–21 September 2015, San Diego, CA.

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http://dx.doi.org/10.1016/j.ijantimicag.2016.04.010
0924-8579/

infectious diseases and, later on, (ii) whether they were associated with an increased risk of adverse events, as stated by a recent publication [7].

2. Methods

2.1. Study setting

Hôpital Raymond-Poincaré is a tertiary teaching hospital with acute care facilities [255 beds, including 43 beds in the adult intensive care unit (ICU)] and a 108-bed rehabilitation unit in Garches (France). There are ca. 8400 admissions per year for complete hospitalisation. The hospital is a centre of expertise in neurological impairment, including spinal cord injured patients, often infected due to their neurological disabilities involving complications such as urinary bladder dysfunction and pressure sores. They are also frequently colonised by MDROs with an incidence that can reach up to twice the expected value in other French healthcare facilities. Hence, in 2011, testing swabs to detect meticillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae colonisation revealed a global incidence density of 0.81 and 1.1 per 1000 patient-days, respectively, compared with 0.38 and 0.46 per 1000 patient-days in the rest of French healthcare facilities [8]. Moreover, in 2013 we reported high antibiotic consumption for inpatients of 672 defined daily doses (DDD) versus 377 DDD per 1000 patient-days in comparison with the rest of French healthcare facilities [9].

In this hospital, antibiotic prescriptions are performed on a computerised physician order entry (CPOE), mostly by residents but also by senior doctors. An Anti-Infective Drug Committee promotes the good use of antimicrobials through educational sessions for physicians, elaboration of intravenous antibiotic administration protocols in the CPOE, and local recommendations for antibiotic prescriptions that are available on a pocket guide for residents (also on the intranet). A referent in infectious diseases provides advice for all hospital departments if needed. He is also in charge of the control of broad-spectrum antibiotics and antibiotic stewardship programmes, including weekly pluridisciplinary meetings involving surgeons and microbiologists.

This prospective *monocentric study* was conducted in Hôpital Raymond-Poincaré among adults hospitalised receiving antibiotics, except for prophylaxis. It concerned all adult departments (orthopaedic surgery, ICU, rehabilitation and medicine).

All ongoing prescriptions were gathered and whether these prescriptions were off-label according to the SPC was assessed.

2.2. Data collection

As a first step, data were collected from February to June 2015 during 11 non-consecutive days to avoid double counting. All prescriptions of antimicrobials were extracted from the CPOE and the following data were recorded by a pharmacist:

- Patient characteristics: name, age, weight, creatinine level (last available) and estimated glomerular filtration rate [Cockcroft–Gault and Modification of Diet in Renal Disease (MDRD) equations];
- Hospital department;
- Antimicrobial: international drug name, posology, route of administration; and
- Therapeutic indication and site of infection.

Consecutively, the therapeutic indication was compared with information issued from the MA as reflected in the SPC. If the indication was in conformity with the SPC, it was further evaluated whether the dose applied (adjusted to renal function) was in accordance with the SPC. If the prescription was off-label regarding the indication, the posology applied was not evaluated.

Hence, each prescription was classified as follows:

- Indication and posology in conformity with the SPC;
- Indication in conformity with the SPC but off-label posology; and
- Off-label indication.

In the case of off-label indication, two infectiologists checked the prescription and compared it with the international guidelines published by scientific societies [Infectious Diseases Society of America (IDSA) and Société de pathologie infectieuse de langue francaise (SPILF)]. These off-label indication prescriptions were then classified as approved or non-approved indications according to the latest guidelines (regardless of whether a first-line or alternative regimen was prescribed).

In the same way, in the case of an off-label dosing, the pharmacist with the help of the infectiologist evaluated whether the posology complied with the guidelines. Then, these off-label posologies were classified as approved or non-approved posologies.

As a second step, in December 2015 all computerised patient files were reviewed and each adverse event (possibly linked with the use of the antimicrobial) notified in these files was recorded.

2.3. Statistical analysis

Statistical analysis was performed to compare rates of adverse events between patients with off-label prescriptions and those with prescriptions in conformity with the SPC. Student's *t*-test was performed to analyse continuous data using GraphPad Prism v.6.0d (GraphPad Software Inc., La Jolla, CA). Statistical significance was defined as $P < 0.05$.

3. Results

A total of 160 antibiotic prescriptions regarding 99 patients with a mean ± standard deviation age of 57.7 ± 17.1 years were analysed. These prescriptions were performed in 31.9% ($n = 51$) of cases in medicine, 31.3% ($n = 50$) in orthopaedic surgery, 25.0% ($n = 40$) in the ICU and 11.9% ($n = 19$) in rehabilitation.

Prescriptions concerned pulmonary infections ($n = 54$; 33.8%), bone and joint infections (BJIs) ($n = 45$; 28.1%), urinary tract infections (UTIs) ($n = 28$; 17.5%), pressure sores ($n = 10$; 6.3%) and other indications ($n = 23$; 14.4%) such as digestive tract infections, endocarditis or other type of skin and soft-tissue infections.

Of 160 prescriptions, 76 (47.5%) were observed to be not in conformity with the SPC, namely 50 off-label indications and 26 off-label doses. Table 1 shows the division of off-label uses according to indications and departments.

The proportion of off-label prescriptions ($n = 76$) varied between departments. Most of them concerned orthopaedic surgery ($n = 26$; 34.2%), rehabilitation ($n = 12$; 15.8%), medicine ($n = 10$; 13.2%) and a few in the ICU ($n = 2$; 2.6%). Depending on the department, off-label prescriptions represented up to 63.2% (12/19) in rehabilitation and 52.0% (26/50) in orthopaedic surgery (Fig. 1).

When considering prescription conformity by site of infection, the majority of off-label uses concerned BJIs ($n = 23$; 30.3%) and UTIs ($n = 14$; 18.4%). When analysing prescription conformity by class of antibiotics, the majority of off-label uses concerned piperacillin/tazobactam ($n = 18$; 23.7%) and glycolipopeptides ($n = 17$; 22.4%) followed by other classes ($n = 18$; 23.7%), including macrolides, trimethoprim/sulfamethoxazole, nitrofurantoin and oral fosfomycin (Fig. 2).

Regarding glycolipopeptide off-label uses, they were due to off-label indications of daptomycin ($n = 8$) and off-label doses of